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(54) Title: ANTI–ANGIOGENIC GENE THERAPY VECTORS AND THEIR USE IN TREATING ANGIOGENESIS–RELATED DISEASES

(57) Abstract

A method for inhibiting tumor growth in a human patient harboring a solid tumor, said method comprising administering to said patient a nucleic acid molecule which expresses in said patient an anti–angiogenic polypeptide selected from the group consisting of human angiostatin, murine angiostatin, human endostatin, murine endostatin, and angiogenesis–inhibiting fragments thereof, wherein expression of the anti–angiogenic polypeptide in the patient inhibits angiogenesis in the vicinity of the tumor and/or systemically by diffusion of the recombinant protein to the vascular compartment from secreting transduced cells, thereby inhibiting its growth.

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ANTI-ANGIOGENIC GENE THERAPY VECTORS AND THEIR USE IN TREATING ANGIOGENESIS-RELATED DISEASES

Field of the Invention

This invention relates generally to gene therapy for, e.g., cancer.

Background of the Invention

Angiogenesis is the process by which new capillaries are formed from existing vasculature. It is a complex process which involves proliferation and migration of endothelial cells. It plays a fundamental role in reproduction, development and wound repair. Unregulated angiogenesis, however, can further the progression of many diseases, including tumor growth and metastasis, arthritis, diabetes, and some forms of blindness. For example, there is experimental evidence that limits of tumor size and growth are not the failure of the tumor cells to proliferate, but rather a failure of the tumor to provide sufficient nutrients and waste removal to its constituent cells by recruiting surrounding vasculature.

Summary of the Invention

The invention features a method for inhibiting tumor growth in a human patient harboring a solid tumor, involving administering to the patient a nucleic acid molecule which expresses in the patient an anti-angiogenic polypeptide selected from the group consisting of human angiostatin, murine angiostatin, human endostatin, murine endostatin, and angiogenesis-inhibiting fragments thereof, wherein expression of the anti-angiogenic polypeptide in the patient inhibits angiogenesis in the vicinity of the tumor and/or systemically by diffusion of the recombinant protein to the vascular compartment from secreting transduced cells, thereby inhibiting its growth.

In a second, related aspect, the invention features tumor inhibition, of

the type just described, using nucleic acids molecules of the formula A-B, where A and B are polypeptide and/or export signal joined by a peptide bond; peptide A contains at least 100 amino acids and includes at least kringles 1, 2, and 3 of human or murine angiostatin; and peptide B contains at least 100 amino acids and includes at least 75% of the amino acid sequence of human or murine endostatin. Expression of the fusion anti-angiogenic polypeptide in the patient inhibits angiogenesis in the vicinity of the tumor and/or systemically by diffusion of the recombinant protein to the vascular compartment from secreting transduced cells, thereby inhibiting its growth. In some embodiments of this hybrid polypeptide and/or export signal method, polypeptide and/or export signal A further includes kringle region 4 of angiostatin, and can also include kringle region 5 of plasminogen (the larger protein molecule of which angiostatin is a portion).

In both aspects of the invention, the nucleic acid molecule preferably constitutes a portion of a viral vector or a plasmid, which can either be administered to the patient so that cells of the patient in the vicinity of the tumor and/or systemically by diffusion of the recombinant protein to the vascular compartment from secreting transduced cells are infected or transfected with the nucleic acid encoding the angiogenesis-inhibiting polypeptide, or cells (of the patient, or another human donor, or an animal) are infected or transfected *ex-vivo*, and those infected or transfected cells are then infused into the patient so that the anti-angiogenic polypeptide is expressed in the vicinity of the tumor and/or systemically by diffusion of the recombinant protein to the vascular compartment from secreting transduced cells.

As will be discussed in more detail below, in particularly effective embodiments, the nucleic acid molecule includes a nucleotide sequence

encoding a preactivation polypeptide and/or export signal for effecting Golgi and/or endoplasmic reticulum export of the anti-angiogenic polypeptide.

In another aspect, the invention features a method for treating a human patient suffering from diabetic retinopathy, involving administering to the patient one of the nucleic acid molecules described above.

The above and other features, objects and advantages of the present invention will be better understood by a reading of the following specification in conjunction with the drawings.

Brief Description of the Drawings

Fig. 1 depicts the structural relationship of angiostatin with plasminogen.

Fig. 2 depicts the structural relationship of endostatin with collagen type XVIII.

Fig. 3 depicts various viral (A. MSCV murine retrovirus; B. Adeno-associated virus; C. HIV based retrovirus; E. recombinant adeno-virus) and non-viral (D. plasmid) vectors used in the construction of gene therapy vectors for this invention.

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D.

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MSCV:	Murine Stem Cell Virus
LTR:	Long Terminal Repeat
RSV:	Rous Sarcoma Virus
ITR:	Inverted Terminal Repeat
HIV:	Human Immunodeficiency Virus
IRES:	Internal Ribosomal Entry Site
GFP:	Green Fluorescence Protein
HBPRE:	Hepatitis B Export Element
RRE:	Rev Response Element
polyA:	polyadenylation site
ψ+:	,,viral packaging sequence

The inverted triangle shows the site at which the anti-angiogenic constructs will be inserted using engineered MluI and XhoI restriction sites.

* denotes specific mutations within the long terminal repeat and leader which bestows the ability for expression in embryonic stem and hematopoietic stem cells.

The arrow denotes the direction of transcription.

Fig. 4 depicts in the left (A) panel nude mice which were implanted with human neuroblastoma cells (line SK-N-AS) transduced with a mock virus and in the right (B) panel, nude mice which were transplanted with human neuroblastoma cells transduced with a retroviral gene therapy vector encoding an angiostatin-endostatin fusion protein.

Fig. 5 shows the nucleotide sequence (SEQ ID NO: 1) and amino

acid sequence (SEQ ID NO: 2) of human plasminogen and the nucleotide sequence (SEQ ID NO: 5) and amino acid sequence (SEQ ID NO: 6) of human angiostatin.

Fig. 6 shows the nucleotide sequence (SEQ ID NO: 9) and amino acid sequence (SEQ ID NO: 10) of murine endostatin.

Fig. 7 shows the nucleotide sequence (SEQ ID NO: 3) and amino acid sequence (SEQ ID NO: 4) of murine plasminogen and the nucleotide (SEQ ID NO: 7) and amino acid sequence (SEQ ID NO: 8) of murine angiostatin.

Detailed Description

This invention provides gene therapy using a vector having a nucleotide sequence encoding one of the above-identified anti-angiogenic polypeptides. Described below in more detail are some of the components of the vectors and methods of the invention.

By a gene therapy vector is meant a vector useful for gene therapy. Gene therapy vectors carry a gene of interest that is useful for gene therapy. The gene therapy vectors are able to be transferred to the cells of an animal, e.g., a human, and are able to express the gene of interest in such cells so as to effect gene therapy. The vector can be, e.g., chromosomal, non-chromosomal, or synthetic, and can be RNA or DNA. The vector can be, e.g., a plasmid, a virus or a phage. Preferred vectors include, e.g., retroviral vectors, adenoviral vectors, adeno-associated vectors, herpes virus vectors, Simliki Forest Virus-based vector, Human Immunodeficiency virus, Simian Immunodeficiency virus, and non-viral plasmids. A preferred retroviral vector is Murine Stem Cell Virus (MSCV), which is a variant of Moloney Murine Leukemia Virus (MoMLV).

By anti-angiogenic polypeptide is meant a polypeptide which inhibits

angiogenesis. The terms polypeptide, protein and polypeptide and/or export signal are used interchangeably herein. By angiogenesis is meant the process by which new vasculature, in particular, new capillaries, are formed from existing vasculature. Angiogenesis is a complex process entailing numerous steps, including local dissolution of the basement membrane, migration of endothelial cells into the surrounding stroma, proliferation of the endothelial cells at the leading edge to form a migrating column of cells, branching and fusion of the newly formed vascular loops, and formation of a new basement membrane. By inhibiting angiogenesis is meant completely or partially inhibiting the formation of such new vasculature.

In certain embodiments, the anti-angiogenic polypeptide is an anti-angiogenic fragment of plasminogen (in particular, angiostatin), an anti-angiogenic fragment of collagen XVIII (endostatin) or a fusion of the two fragments.

Angiostatin is an internal fragment of plasminogen having a molecular weight of 38 or 45 kDa, depending on whether it contains kringles 1-3 or 1-4. In the invention, either can be used, or a molecule including kringles 1-3 and a portion of kringle 4 can be used. Angiostatin can be naturally produced in vivo in small amounts by tumor cells, e.g. murine Lewis lung carcinoma cells, by proteolytic cleavage of plasminogen so as to eliminate the N-terminal portion including the signal polypeptide and/or export signal and the preactivation polypeptide and/or export signal, as well as the C-terminal portion following kringle 3 or 4. Mouse and human angiostatin have been purified and sequenced. In preferred embodiments, the gene therapy vectors of this invention encode angiostatin having kringles 1, 2 and 3, or angiostatin having kringles 1, 2, 3 and 4.

In another preferred embodiment, the anti-angiogenic polypeptide is

endostatin or a biologically active analog or fragment thereof. Endostatin can be naturally produced *in vivo* in small amounts by tumor cells, e.g., murine angiosarcoma cells, by proteolytic cleavage of endogenous collagen XVIII so as to eliminate the N-terminal portion including the signal polypeptide and/or export signal and the preactivation polypeptide and/or export signal, as well as the C-terminal portion following kringle 3 or 4. See Fig.2. Mouse endostatin has been sequenced, and the human molecule (SEQ ID NOs: 17 and 18) forms a portion of collagen 18 (SEQ ID NOs: 19 and 20).

The human molecule position and sequence are apparent from an alignment of the active, Lys-terminated active region of human collagen 18 with murine endostatin, such that the C-terminal lysine residues align, bringing the active endostatin sequences into alignment.

In yet another preferred embodiment, the anti-angiogenic polypeptide is an in-frame fusion of angiostatin or a biologically active analog or fragment thereof and endostatin or a biologically active analog or fragment thereof. Preferably, the angiostatin or biologically active analog or fragment is 5' of the endostatin or biologically active analog or fragment. In certain embodiments, the angiostatin-endostatin fusion proteins exhibit synergistic anti-angiogenic properties.

By fragment is meant some portion of the naturally occurring anti-angiogenic polypeptide. Preferably, the fragment is at least 20 amino acid residues, more preferably at least 50 amino acid residues, and most preferably at least 100 amino acid residues in length. Fragments include chimeric constructs composed of at least a portion of the relevant gene and another molecule. The ability of a candidate fragment to exhibit a biological activity of the anti-angiogenic polypeptide can be assessed by methods known to those skilled in the art, e.g., by its ability to inhibit proliferation of bovine capillary

cells, or by its ability to inhibit growth of primary tumor cells, e.g., as described herein. See, e.g., Example 9. Also included are fragments containing residues that are not required for biological activity of the fragment or that result from alternative mRNA splicing or alternative protein processing events.

Internal or terminal fragments of a polypeptide can be generated by removing one or more nucleotides from one end (for a terminal fragment) or both ends (for an internal fragment) of a nucleic acid which encodes the polypeptide.

In preferred embodiments, the gene therapy vector of this invention is capable of hybridizing to the native anti-angiogenesis polypeptide-encoding regions and has at least about 80%, preferably at least about 90%, and more preferably at least about 95%, sequence identity to the native nucleotide sequences, and encodes a polypeptide which has anti-angiogenic activity; or a biologically active fragment of any of the above nucleotide sequences wherein the encoded polypeptide has anti-angiogenic activity.

The nucleotide sequences of the present invention can be in the form of RNA or DNA, and the nucleotide sequence can be double-stranded or single stranded and, if single stranded, can be the coding strand or non-coding (anti-sense) strand.

The coding sequence which encodes the anti-angiogenic polypeptide can be identical to the native coding sequences, or can be a different coding sequence which, as a result of the degeneracy of the genetic code, encodes the same anti-angiogenic polypeptide.

In certain embodiments, the gene therapy vector also has a nucleotide sequence encoding a signal polypeptide and/or export signal (SP) for effecting secretion of the anti-angiogenic polypeptide. Examples of signal polypeptide and/or export signal include plasminogen signal polypeptide and/or export

signal. Preferably, the signal polypeptide and/or export signal is 5' (i.e., upstream) of the nucleotide sequence encoding the anti-angiogenic polypeptide.

Preferably, the gene therapy vector has a nucleotide sequence encoding a preactivation polypeptide and/or export signal (PAP), which is a small polypeptide and/or export signal which effects folding and secretion of the anti-angiogenic polypeptide *in vivo*. Examples of preactivation polypeptide and/or export signal include plasminogen preactivation polypeptide and/or export signal, described herein, and PAP's of other proteins in the blood clotting cascade.

Preferably, the preactivation polypeptide and/or export signal is positioned 5' of the nucleotide sequence encoding the anti-angiogenic polypeptide. In embodiments which have a signal sequence and an anti-angiogenic polypeptide, preferably the preactivation polypeptide and/or export signal is 5' of the nucleotide sequence encoding the anti-angiogenic polypeptide, and 3' of the nucleotide sequence encoding the signal polypeptide and/or export signal.

We have discovered that results obtained using constructs containing a PAP- encoding nucleic acid sequence are far superior to results using constructs lacking a PAP-encoding sequence. Our hypothesis to explain these unexpectedly superior results with PAP is that, during the complex process by which the anti-angiogenic polypeptide is expressed and processed in living cells, the PAP polypeptide and/or export signal facilitates the export of the polypeptide from the cellular Golgi apparatus and/or the endoplasmic reticulum (ER). The corollary is that, absent PAP, a significant portion of the expressed polypeptide remains trapped in the Golgi and/or ER.

The PAP exemplified herein is derived from human plasminogen; this

PAP is currently preferred. Our discovery that the use of a PAP dramatically improves results leads us to believe that other PAP's would be useful as well, and such others are therefore contemplated for use in the invention. Thus, as used herein, "PAP" refers to a polypeptide and/or export signal which is naturally associated with a eukaryotic (preferably human) protein, the exportation of which is facilitated by its associated PAP. Examples of other human proteins whose Golgi/ER export is PAP-facilitated include other secreted proteins of the blood coagulation cascade, e.g., fibrinogen, prothrombin, Factor VIII, and Factor IX. Other secreted human proteins also are associated with potentially useful PAPs.

It is not essential that the PAP used in the invention be identical in amino acid sequences to a native PAP; it is well-known that polypeptide and/or export signal that facilitate protein secretion or export, e.g., signal polypeptide and/or export signal and PAPs, can vary from the native forms to a certain extent and still retain their function. Therefore, PAPs useful according to the invention preferably have 75% or greater amino acid sequence identity with a native PAP.

In certain embodiments, the gene therapy vector has a nucleotide sequence encoding a tag for identification of the anti-angiogenic polypeptide and/or export signal. In certain embodiments, the tag is 5' of the nucleotide sequence encoding the anti-angiogenic polypeptide; in other embodiments, the tag is 3' of the nucleotide sequence encoding the anti-angiogenic polypeptide. In embodiments in which the anti-angiogenic polypeptide is endostatin or an angiostatin-endostatin fusion, it is preferred that the tag be 5' of the nucleotide sequence encoding endostatin.

In certain embodiments the gene therapy vector includes a selectable

marker, e.g., a Neomycin phosphotransferase gene, or a humanized red-shifted green fluorescent protein.

The invention also includes a cell infected or transfected with a gene therapy vector described herein. Preferably, the cell is an animal cell, more preferably an autologous or allogeneic human cell. The gene therapy vectors described herein can be introduced into a cell, e.g., by transformation, transfection, transduction, infection, or ex vivo injection. They can be targeted to a particular cell type.

Administration of nucleic acid, e.g., a gene therapy vector, can be accomplished by any method which allows the nucleic acid to reach the target cells. These methods include, e.g., injection, deposition, implantation, suppositories, oral ingestion, inhalation, topical administration, or any other method of administration where access to the target cells by the nucleic acid is achieved. Injections can be, e.g., intravenous, intradermal, subcutaneous, intramuscular or intraperitoneal. Implantation includes inserting implantable drug delivery systems, e.g., microspheres, hydrogels, polymeric reservoirs, cholesterol matrices, polymeric systems, e.g., matrix erosion and/or diffusion systems and non-polymeric systems, e.g., compressed, fused or partially fused pellets. Suppositories include glycerin suppositories. Oral ingestion doses can be enterically coated. Inhalation includes administering the nucleic acid with an aerosol in an inhalator, either alone or attached to a carrier that can be absorbed.

In certain embodiments of the invention, administration can be designed so as to result in sequential exposures to the nucleic acid over some time period, e.g., hours, days, weeks, months or years. This can be accomplished by repeated administrations of the nucleic acid, e.g., by one of the methods described above, or alternatively, by a controlled release delivery system in

which the nucleic acid is delivered to the animal over a prolonged period without repeated administrations. By a controlled release delivery system is meant that total release of the nucleic acid does not occur immediately upon administration, but rather is delayed for some time. Release can occur in bursts or it can occur gradually and continuously. Administration of such a system can be, e.g., by long acting oral dosage forms, bolus injections, transdermal patches or subcutaneous implants. Examples of systems in which release occurs in bursts include, e.g., systems in which the nucleic acid is entrapped in liposomes which are encapsulated in a polymer matrix, the liposomes being sensitive to a specific stimulus, e.g., temperature, pH, light, magnetic field, or a degrading enzyme, and systems in which the nucleic acid agent is encapsulated by an ionically-coated microcapsule with a microcapsule core-degrading enzyme. Examples of systems in which release of the nucleic acid is gradual and continuous include, e.g., erosional systems in which the nucleic acid is contained in a form within a matrix, and diffusional systems in which the nucleic acid permeates at a controlled rate, e.g., through a polymer. Such sustained release systems can be, e.g., in the form of pellets or capsules.

The nucleic acid is administered to the patient in a therapeutically effective amount. By therapeutically effective amount is meant that amount which is capable of at least partially preventing or reversing the disease. A therapeutically effective amount can be determined on an individual basis and will be based, at least in part, on consideration of the patient's size, age, the efficacy of the particular nucleic acid used, the type of delivery system used, the time of administration relative to the onset of disease symptoms, and whether a single, multiple, or controlled release dose regimen is employed. A therapeutically effective amount can be determined by one of ordinary skill in the art employing such factors and using no more than routine experimentation.

In certain embodiments, a therapeutically effective amount of an anti-angiogenic polypeptide is administered by providing to the animal a nucleic acid encoding the polypeptide and expressing the polypeptide in vivo. Nucleic acids encoding the polypeptide, or mutants thereof, can be administered in any biologically effective carrier, e.g. any formulation or composition capable of effectively delivering the nucleotide sequence for the anti-angiogenic polypeptide to cells in vivo. Approaches include, e.g., insertion of the nucleic acid into viral vectors. Viral vectors can be delivered to the cells, e.g., by infection or transduction using the virus. Viral vectors can also be delivered to the cells, e.g., by physical means, e.g., by electroporation, lipids, cationic lipids, liposomes, DNA gun, $Ca_3(PO_4)_2$ precipitation, or delivery of naked DNA. In certain preferred embodiments, the virus is administered by injection, e.g., intramuscular injection, in a dose range of about 10^3 to about 10^{10} infectious particles per injection, more preferably in a dose range of about 10^5 to about 10^8 infectious particles per injection. Single or multiple doses can be administered over a given period of time, depending, e.g., upon the disease.

An alternative is insertion of the nucleic acid encoding the anti-angiogenic polypeptide into a bacterial or eukaryotic plasmid. Plasmid DNA can be delivered to cells with the help of, e.g., cationic liposomes (lipofectin™; Life Technologies, Inc., Gaithersburg, MD) or derivatized (e.g., antibody conjugated) polylysine conjugates, gramacidin S, artificial viral envelopes or other such intracellular carriers, as well as direct injection of the gene construct or $Ca_3(PO_4)_2$ precipitation carried out in vivo, or by use of a gene gun. The above-described methods are known to those skilled in the art and can be performed without undue experimentation.

Since transfer of the nucleic acid to appropriate target cells represents the critical first step in gene therapy, choice of the particular gene delivery

system will depend on such factors as the intended target and the route of administration, e.g., locally or systemically. Targets for delivery of the nucleic acid can be, e.g., specific target cells which are diseased. For example, the target can be, e.g., the peritoneal cavity, gastro-intestinal tract, bone marrow cavity, liver, lungs, muscles, vasculature, pericardial cavity, pleural cavity, skin, sub-cutaneous or deep connective tissues, central nervous system, spinal fluid, eye, or specific sites of tumor growth. Administration can be directed to one or more cell types, and to one or more cells within a cell type, so as to be therapeutically effective, by methods known to those skilled in the art. For example, the nucleic acid can be, e.g., coupled to an antibody, to a ligand to a cell surface receptor, or to a toxin component, or can be contained in a particle which is selectively internalized into cells, e.g., liposomes, or a virus where the viral receptor binds specifically to a certain cell type, or a viral particle lacking the viral nucleic acid, or can be administered by local injection.

In certain embodiments, the nucleic acid is administered to the patient by introducing *ex vivo* the nucleic acid into cells of the patient, or into syngeneic or allogeneic or xenogeneic cells, and then administering the cells having the nucleic acid to the animal. Any cell type can be used. In certain embodiments, the cells having the introduced nucleic acid are expanded and/or selected after the nucleic acid transfer. The cells having the transferred nucleic acid are subsequently administered to the patient. Preferably, the cells are administered in a dose range of about 1×10^6 to about 1×10^9 cells/dosage/day, and most preferably at about 1×10^7 to about 1×10^8 cells/dosage/day. The cells can be administered by any method which results in delivering the transferred nucleic acid in the cells to the desired target. For example, the cells can be implanted directly into a specific tissue of the patient, or implanted after encapsulation within an artificial polymer matrix. Examples of sites of

implantation include, e.g., the peritoneal cavity, gastro-intestinal tract, bone marrow cavity, liver, lungs, muscles, vasculature, pericardial cavity, pleural cavity, skin, sub-cutaneous or deep connective tissues, central nervous system, spinal fluid, eye, or specific sites of tumor growth.

Systemic delivery can be achieved, e.g., by introducing the nucleic acid into cells which circulate in the peripheral blood of the patient, or which give rise to cells which circulate in the peripheral blood. In certain embodiments, the nucleic acid is introduced into such cells *ex vivo*, and these cells are then administered to the patient, resulting in systemic delivery within the peripheral blood. These cells can be the cells of the patient or allogeneic cells. Preferred cells in which the nucleic acid can be introduced are hematopoietic cells.

In certain embodiments, other therapy is additionally administered. For example, if the animal is being treated for a tumor, other tumor therapy, e.g., another therapeutic agent, chemotherapy, radiation or surgery, is additionally administered to the patient, either simultaneously or at different times.

Treating is meant to include, e.g., preventing, treating, reducing the symptoms of, or curing the disease. I.e. treating a tumor includes preventing growth of the tumor, causing shrinkage of the tumor, or preventing development of micro-metasteses.

Preferably, the recombinant nucleic acid is a gene therapy vector, e.g., as described herein. Preferably, the anti-angiogenic polypeptide is angiostatin, endostatin, an angiostatin-endostatin fusion protein, or biologically active analogs or fragments thereof. In certain embodiments, the angiostatin has kringles 1, 2 and 3; in other embodiments, the angiostatin has kringles 1, 2, 3 and 4, and, in some embodiments, kringle 5 of human or murine plasminogen. Angiostatin is described in O'Reilly and Folkman U.S. Patent No. 5,639,725, hereby incorporated by reference. Endostatin is described in O'Reilly and

Folkman PCT Appln. No. WO 97/15666, published May 1, 1997, hereby incorporated by reference.

In certain embodiments, the recombinant nucleic acid has been introduced *ex vivo* into cells so as to express the anti-angiogenic polypeptide in the cells, and the recombinant nucleic acid is administered to the patient by administering to the patient the cells containing the recombinant nucleic acid. In certain embodiments, the cells are derived from the patient; in other embodiments the cells are allogeneic cells relative to the cells of the patient.

Where cells are infected or transfected *ex vivo* for later infusion into the patient, the cells are preferably hematopoietic cells, but can also be mesenchymal cells, stem cells, epithelial cells (e.g., from the gut), or dendritic cells.

The gene therapy vectors of the invention can be provided in a pharmaceutical composition comprising a therapeutically effective amount of the recombinant nucleic acid together with a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers include, e.g., water, saline, dextrose, glycerol, ethanol, liposomes and lipid emulsions.

The following non-limiting examples further illustrate the present invention.

EXAMPLES

Example 1: Construction of Inserts for Gene Therapy Vectors Containing cDNA for Angiostatin, Endostatin or Angiostatin-Endostatin Fusion Proteins

The following genetic constructs are inserted into retroviral gene therapy vectors; the genetic constructs contain human or murine cDNA for angiostatin, endostatin or an angiostatin-endostatin fusion, and DNA encoding a signal

polypeptide and/or export signal (SP), a tag (FLAG), and, preferably, a preactivation polypeptide and/or export signal (PAP). The constructs are all made using standard genetic engineering techniques, and their insertion into retroviral gene therapy vectors is carried out using known methods. The constructs have the following components:

Murine Constructs
SP-K1-K2-K3-Flag
SP-K1-K2-K3-K4-Flag
SP-K1-K2-K3-K4-K5-Flag
SP-PAP-K1-K2-K3-Flag
SP-PAP-K1-K2-K3-K4-Flag (SEQ ID NO: 11 and 12)
SP-Flag-Endo (SEQ ID NO: 13 and 14)
SP-K1-K2-K3- Flag-Endo
SP-K1-K2-K3-K4- Flag-Endo (SEQ ID NO: 15 and 16)
SP-PAP-K1-K2-K3- Flag-Endo

Human Constructs
SP-K1-K2-K3
SP-K1-K2-K3-K4
SP-K1-K2-K3-K4-K5
SP-PAP-K1-K2-K3
SP-PAP-K1-K2-K3-K4
SP-PAP-K1-K2-K3-K4-K5
SP-Endo
SP-K1-K2-K3-Endo
SP-PAP-K1-K2-K3-Endo

Nucleic acid and amino acid sequences for mouse and human angiostatin and endostatin used in these constructs are shown in Figs. 5-7.

Nucleic acid and amino acid sequence of the FLAG peptide:

amino terminus-	ASP	TYR	LYS	ASP	ASP	ASP	ASP	LYS
5'-	GAC	TAC	AAG	GAC	GAC	GAT	GAC	AAG

Human plasminogen derivative constructs

The entire coding region of the human plasminogen cDNA from the start (ATG) to the stop (TAA) codon is 2433bp in size.

This sequence encodes a signal peptide (bp 1-57), a preactivation peptide (bp 58-288), and 5 distinct structural regions known as kringles (K1-K3 from bp 289-1092; K4 from bp1093-1380; K5 from bp 1381-1740). Please note that although I have given precise bp measurements for kringles K4 and K5, it can be argued that the sequence encoding K4 is between bp1056-1440 and the sequence encoding K5 is between bp1362-1680.

A DNA fragment encoding a portion of the human plasminogen protein from bp 1 to 1377 was obtained by PCR of a widely available human liver cDNA library using synthetic DNA oligonucleotides complementary to sequences immediately preceding the signal peptide and immediatly following kringle 4. This fragment contains the sigal peptide (bp1-57), the preactivation peptide (bp 58-288), kringles 1 (bp289-549), 2 (bp 550-804), 3 (bp 805-1092) and 4 (bp 1093-1380). The synthetic oligonucleotides used for this reaction contained engineered recognition sites for the restriction enzymes EcoRI and XhoI. Following the PCR reaction the amplified fragment was cloned into the EcoRI/XhoI sites of BluescriptSK(-) (Stratgene) using standard techniques (Maniatis). Following cloning the integrity of the amplified sequence was verified by sequencing both strands using the Sanger method (Sanger). Various derivatives of the cloned fragment were subsequently constructed using BluescriptSK(-) (Stratagene) as a backbone. A full list of the derivatives are described in Table 1. Briefly, the variations are composed of constructs containing various combinations of kringles with or without the signal and/or preactivation peptide sequences. These derivatives were constructed using both standard techniques as well as PCR and the use of double stranded synthetic oligonucleotides. In all cases the integrity of the start codon, coding sequence and termination codon was verified by double stranded sequencing using the Sanger method.

Murine plasminogen derivative constructs

The coding sequence for murine plasminogen is 2439bp in size and, similar to the human plasminogen cDNA encompasses a sequence encoding signal and preactivation peptides (bp 1-57 and 58-288 respectively) in addition to 5 kringle regions; kringle 1-3 (bp 289-1092), kringle 4 (bp 1093-1380) and kringle 5 (bp 1381-1743). Again, although I have given precise bp measurements for kringles K4 and K5, it can be argued that the sequence encoding K4 is between bp1056-1440 and the sequence encoding K5 is between bp1362- 1680.

The murine plasminogen cDNA has previously been cloned and was made available to us. Derivatives of murine plasminogen were constructed using sequences derived from bp 1-1743 of the coding sequence. Various combinations of kringle regions with or without signal and preacivation peptide regions were made using BluescriptSK(-) (Stratagene, La Jolla, CA) as the vector backbone. These derivatives were constructed using standard cloning techniques (Maniatis, Molecular cloning; a laboratory manual, second edition, 1989) in combination with PCR utilizing synthetic oligonuleotides using

Angiostatin function was not altered by adding the FLAG polypeptide and/or export signal to either the N- or C-terminal ends, whereas endostatin was functional only if FLAG was added to its N-terminal end.

Example 2: Construction of Retroviral Gene Therapy Vectors

This example illustrates the construction of retroviral gene therapy vectors comprising cDNA for angiostatin, endostatin or angiostatin-endostatin fusion proteins.

The DNA inserts from Example 1 were inserted into two retroviral vectors. Both vectors were derived from the Murine Stem Cell Virus (MSCV), which is a variant of Moloney Murine Leukemia Virus (MoMLV) having several mutations allowing high, sustained expression in hematopoietic stem cells and their progeny. In both cases, the angiostatin, endostatin, or angiostatin-endostatin fusion DNA inserts were under the transcriptional control of the retroviral left Long Terminal Repeat (LTR). In the first vector, the dominant selectable marker was the Neomycin phosphotransferase gene (NeoR), which confers resistance to G418, and is driven by an internal phosphoglycerate kinase (PGK) promoter. In the second vector, the dominant selectable marker was the humanized, red-shifted green fluorescent protein (EGFP), which is co-translationally expressed by means of an Internal Ribosome Entry Site (IRES) from the Encephalomyocarditis virus (EMCV).

The retroviral gene therapy vectors were transfected by $CaPO_4$ precipitation in the transient ecotropic packaging cell-line BOSC 23, Pear et al., *PNAS* 90:8392 (1993). Viral supernatants were collected two days thereafter and filtered through 0.45 mm filters. Filtered viral supernatants were subsequently used to infect GENETIX's stable amphotropic retroviral packaging cell-line AM12 (Genetix Pharmaceuticals, Inc., Cambridge, MA). After another two days, viral supernatants from transduced AM12 were filtered

and used to infect GENETIX's stable ecotropic retroviral packaging cell-line GP+E86 (Genetix Pharmaceuticals, Inc.). Both transduced AM12 and GP+E86 were then selected in the presence of G418 (in the case of constructs bearing NeoR) or sorted by Fluorescent Activated Cell Sorter (FACS) for EGFP expression. Viral titers were estimated according to standard practice by counting G418 resistant colonies among NIH3T3 cells exposed to diluted virus preparation. Ecotropic viral titers were above 5 x 10^5 /ml of viral supernatants, only 3-fold lower than "empty" control vectors. No Replication Competent Retrovirus (RCR) was detected in standard assays.

Example 3: Transduction of Target Cells Using Retroviral Gene Therapy Vectors

This example illustrates the stability of retroviral gene therapy vector transmission and the lack of toxicity in non-endothelial target cells.

Following 24-hour incubation of confluent viral producer cells in 100 mm plates, viral supernatant was removed and filtered (0.45 μm filter, Gelman Sciences, Ann Arbor, MI). Viral supernatant, containing 7 μg/ml polybrene (Sigma, St. Louis, MO), was added to target cells 24 hours after plating the target cells. Fresh medium was added after 4-12 hours, and, after an additional 48 hours, cells were selected for retroviral infection by exposure to medium containing 1 mg/ml G418 (Gibco BRL, Grand Island, NY) or by FACS sorting (FACStar cell sorter, Becton Dickinson, San Jose, CA). The stability of transmission of the retroviral gene therapy vectors described in Example 2 was examined by Southern blot analysis of transduced NIH3T3 cells, using specific probes (EGFP) and restriction enzyme digestion of genomic DNA with Sac1, which cuts only once in each LTR. Stable chromosomal integration of intact proviruses of appropriate length was observed with all constructs.

The lack of non-specific toxicity on non-endothelial cells was

established by using filtered viral supernatants to transduce various tumor cell-types and cell-lines (NIH3T3 cells, K562 cells (ATCC), and human SK-N-AS neuroblastoma cells; Cohen, P.S., *Cancer Research*, 55:2380 (1995). Transduced cell populations were subsequently selected with G418 or sorted for EGFP expression by FACS. No obvious effects on cell viability, growth or other phenotypical characteristics were detected.

Example 4: Protein Expression of Angiostatin, Endostatin and Angiostatin-Endostatin Fusion Proteins in Cells Transduced with Retroviral Gene Therapy Vectors

This example illustrates that recombinant angiostatin, endostatin, and angiostatin-endostatin fusion proteins were readily detected in retrovirally transduced cells and their supernatant, indicating efficient expression and secretion.

MSCV virus based vectors containing sequences encoding murine Kringle 1 (K1), K1K5, K1K2K3, K1K2K3K4, and K1K2K3K4K5 were used to transduce NIH3T3 cells. With regard to the murine recombinant proteins, Western blot analysis of transduced cells and their supernatant was performed by means of a monoclonal antibody that recognizes the FLAG polypeptide and/or export signal. Because this antibody is not mono-specific, significant cross-reactivity with murine proteins was apparent. However, by comparing the pattern obtained with mock cells, it was clear that the antibody revealed an additional band of appropriate size in all transduced cells. Moreover, the recombinant proteins were detected in cell supernatants at levels above 50 ng/ml, using a protein concentration/semi-purification procedure (Centricon columns, Amicon, Beverly, MA). With regard to the human recombinant proteins, no FLAG tag was added, so a monoclonal antibody that recognizes specifically the first three kringles of human plasminogen in its native, non-

denatured form was used; O'Reilly et al., *Cell* 79:315 (1994). Because of this constraint, Western blot analysis using denaturing gels could not be performed. An ELISA assay was performed which indicated that human recombinant angiostatin was detected at levels likely to be therapeutic according to previous findings in the model of Lewis Lung Carcinoma *Id.*

These results indicate that high levels of recombinant proteins of expected length were expressed in retrovirally transduced cells and were efficiently secreted.

Example 5: In Vivo Anti-Tumor Activity of Cells Transduced with Gene Therapy Vectors Encoding the Angiostatin-Endostatin Fusion Protein

Human SK-N-AS neuroblastoma cells (Cohen, 1995) were transduced with the retroviral gene therapy vector containing the angiostatin-endostatin fusion protein, described in Example 2. These cells (1,000,000) were suspended in 1 mL Dulbecco's phosphate buffered saline and injected into the right mid-quadrant of nude immuno-compromised mice. While no impairment of the in vitro growth of transduced cells was observed, a dramatic decrease in tumor growth in nude mice cells following subcutaneous implantation of the transduced cells was evident as compared to "mock virus"-transduced control cells.

Example 6: Ex Vivo Transfer of Retroviral Gene Therapy Vectors Encoding Anti-Angiogenic Polypeptides to Primary Hematopoietic Cells, and Subsequent Transplantation to Recipient Mice

This example illustrates infection of primary hematopoietic cells from

donor mice with retroviral gene therapy vectors encoding angiostatin, endostatin, or an angiostatin-endostatin fusion protein, and a selectable GFP marker, and subsequent transplantation of the transduced hematopoietic cells into recipient mice.

Femoral bone marrow cells are harvested from male donor C57BL6/J-Ly5.1 mice (Jackson Labs, Bar Harbor, ME), intravenously injected four days previously with 150 mg/kg of 5-fluorouracil (5-FU). Bone marrow cells are cultured for two days in medium composed of DMEM, 15% fetal calf serum, 10 ng/ml human IL-6, 6 ng/ml murine IL-3 and 100 ng/ml murine Steel factor prior to two days of culture atop a confluent monolayer of irradiated (1,500 cGy, ^{137}Cs γ-irradiation) viral producer cells in the above medium including 6 ug/ml of prolamine sulfate. The viral producer cells are transfected with a retroviral gene therapy vector, as described above. Upon completion of the co-culture infection protocol, recovered non-adherent cells are cultured for an additional 48 hours to allow for expression of the transferred GFP gene. Retrovirally transduced cells expressing the transferred GFP gene are subsequently identified and selected for, using a FACStar+ cell sorter (Becton Dickinson, San Jose, CA). The GFP+ cells are intravenously injected into congenic female C57BL6/J-Ly5.2 recipient mice (National Cancer Institute, Washington, DC) previously given 950 cGy (83cGy/min, ^{137}Cs γ-rays) of whole body irradiation. In each case, a small fraction of GFP+ sorted cells is used for day 12 CFU-S and in vitro clonogenic progenitor assays to assess the efficiency of the infection and selection procedures on these more mature cell types.

Example 7: Engraftment of Recipient Mice with Donor-Derived Hematopoietic Cells

This example illustrates engraftment of the recipient mice with the

donor-derived transfected hematopoietic cells from Example 6.

The donor and recipient mice are phenotypically distinguishable on the basis of Y chromosome specific sequences, as well as on the basis of allelic differences at the murine CD45 cell surface antigen locus. Male donor mice are homozygous for the CD45.2 allele, while female recipient mice are homozygous for CD45.1. The engraftment of recipient mice with donor-derived (CD45.2+) cells is assessed at both short (5 weeks) and long (34 months) time points post-transplant by flow cytometric analysis of peripheral blood samples stained with a phycoerythrin labeled antibody specific for the CD45.2 antigen (Pharmingen, San Diego, CA). The results indicate that engraftment occurs.

Example 8: Proviral Marking and GFP Expression in Recipient Mice

This example illustrates the presence of recombinant provirus and expression of the transferred GFP gene in the recipient mice from Example 6.

The level of proviral marking in reconstituted animals is initially determined by Southern blot and semi-quantitative PCR analysis of DNA obtained from peripheral blood leukocytes. The large majority of donor-derived (CD45.2+) cells in recipient mice contain a minimum of one copy of recombinant provirus. In addition, flow cytometric analysis of peripheral blood leukocytes is performed to ascertain the proportion of cells expressing the transferred GFP cDNA. Because the GFP and angiogenic inhibitor protein cDNAs are both driven from the same regulatory sequences, due to the inclusion of an internal ribosomal entry site (IRES) element, the analysis of GFP expression in the peripheral blood provides an indirect measurement of the levels of anti-angiogenic protein being expressed. The results indicate expression of the transferred genes.

Example 9: Anti-Angiogenic Polypeptide Expression in Recipient Mice

This example illustrates the presence of anti-angiogenic polypeptide in the sera of the recipient mice from Example 6, using both physical and functional assays.

Serum obtained from the transplanted animals described in Example 6 is used for ELISA using an antibody specific for the synthetic FLAG epitope (IBI, Eastman Kodak, New Haven, CT) and compared against known standards of purified protein. Results indicate the presence of the anti-angiogenic polypeptide in the serum.

To determine whether a functional anti-angiogenesis polypeptide is present in the circulation, sera from transplanted animals is tested for its ability to inhibit the proliferation of bovine capillary cells *in vitro;* O'Reilly (1994). Briefly, cells are plated in 24 well dishes at 25,000 cells/ml and maintained in DMEM with 5% bovine calf serum for 24 hours. The medium is then replaced with fresh medium containing various dilutions of the test serum. After 20 minutes of incubation, fresh medium including b-FGF (final concentration 1 ng/ml) is added and the cells are cultured for 72 hours. Cells are then dispersed using trypsin and the cell number determined by Coulter counter. Results indicate that functional anti-angiogenic polypeptide is present in the sera of the recipient mice.

In addition, the ability of circulating anti-angiogenic polypeptide to inhibit the growth of primary tumor cells is assessed. Transplanted mice are subcutaneously injected with one million Lewis lung carcinoma (LLC) cells (O'Reilly, (1994)) at the proximal midline of their dorsal skin. The mice are closely monitored for survival, tumor size and growth, and overall health. Results indicate that the anti-angiogenic polypeptides from the sera of the

recipient mice inhibit growth of the LLC tumor cells.

Finally, upon sacrifice of the transplanted recipient mice, blood, spleen, thymus and bone marrow are harvested and analyzed for the presence of proviral DNA by Southern analysis as well as expression of the transferred GFP and anti-angiogenic polypeptide cDNAs by flow cytometry and ELISA. Moreover, a portion of bone marrow cells is re-transplanted into secondary recipients to generate individual day 12 spleen colonies, as well as plated in methylcellulose to assess in vitro clonogenic progenitors. Individual clones are analyzed for proviral DNA by PCR or Southern blot, and for gene expression by flow cytometry and ELISA. Results of these tests also indicate the presence of proviral DNA and expression of the anti-angiogenic polypeptides and marker proteins.

Example 10: Evaluating the Efficacy of Retroviral Gene Therapy Vectors Encoding Anti-Angiogenic Polypetides on Various Human Cancers Implanted in SCID Mice Using Ex Vivo Gene Therapy

This example illustrates a method for rapidly screening various forms of human cancer to determine susceptibility to treatment by the systemic delivery of anti-angiogenic polypeptides.

The methods for gene transfer, assessment of proviral marking and assessment of transferred gene expression as described in Examples 3 through 9 are repeated using immuno-deficient SCID mice, with the following exceptions. Since SCID mice are more sensitive to γ-irradiation than C57BL6/J mice, the female SCID recipients receive a lower dose of 400cGy of whole body irradiation in contrast to the 950cGy required for C57BL6/J. In addition, since the SCID mice do not possess allelic differences at the CD45 cell surface antigen locus, donor and recipient cells are phenotypically distinguished on the basis of Y chromosome specific sequences using Southern

blot analysis.

Bone marrow from male donor SCID mice is infected, selected for on the basis of expression of the transferred GFP marker cDNA, and transplanted into irradiated female SCID recipients. Engraftment with provirally marked cells and expression of the transferred genes is demonstrated. The mice are then separately implanted with a variety of human tumor cell types, e.g., breast adenocarcinoma, lung squamous cell carcinoma, and brain glioblastoma. In each case, the ability of the anti-angiogenic polypeptides to inhibit the growth of the various human tumor cell types is monitored and quantified.

Example 11: Evaluating the Efficacy of Retroviral Gene Therapy Vectors Encoding Anti-Angiogenic Polypeptides for Treatment of Ovarian Cancer Using In Vivo Gene Therapy

This example illustrates the feasibility of using retroviral gene therapy vectors encoding anti-angiogenic polypeptides to achieve efficient gene transfer to established tumors in vivo using a well-established murine model of human ovarian cancer. Following injections, mice are closely monitored for tumor growth and survival.

Eight to ten week old nude mice (Jackson Labs, Bar Harbor are injected intra-peritoneally with 1 x 10^7 PA-1 cells, an ovarian cancer cell-line (ATCC), and followed until palpable tumors are identified. Viral supernatant for in vivo injection is prepared as follows: Viral producer cells are grown to confluence in DMEM with 10% bovine calf serum, and the medium is then changed. After 24 hours of incubation, the viral conditioned supernatant is filtered though a 0.45 um low protein binding filter, protamine sulfate is added to a final concentration of 6ug/ml, the solution is aliquoted into 2 ml volumes, and frozen at -80°C. Recipient mice receive three intraperitoneal injections of viral supernatant (2 mls per injection) in addition to the polycation, over a period of

36 hours. Control mice are injected with medium collected from confluent dishes of NIH3T3 cells. Following injection of the viral conditioned supernatant, the mice are analyzed for survival as well as tumor growth over time as compared to mock injected controls. Results indicate that treatment of the ovarian cancer occurs. At death, the tumors are removed, weighed, and the cells dissociated for DNA extraction for Southern blot analysis to detect recombinant provirus.

Those skilled in the art will be able to ascertain using no more than routine experimentation, many equivalents of the specific embodiments of the invention described herein. These and all other equivalents are intended to be encompassed by the following claims.

In other embodiments, the invention provides methods and compositions for treating diseases and processes that are mediated by angiogenesis including, but not limited to, hemangioma, solid tumors, leukemia, metastasis, telangiectasia, psoriasis, scleroderma, pyogenic granuloma, myocardial angiogenesis, plaque neovascularization, coronary collaterals, cerebral collaterals, arteriovenous malformations, ischemic limb angiogenesis, corneal diseases, rubeosis, neovascular glaucoma, diabetic retinopathy, retrolental fibroplasia, arthritis, diabetic neovascularization, macular degeneration, wound healing, peptic ulcer, *Helicobacter* related diseases, fractures, keloids, vasculogenesis, hematopoiesis, ovulation, menstruation, placentation, and cat scratch fever.

What is claimed is:

CLAIMS

1. Use of a nucleic acid molecule which expresses an anti-angiogenic polypeptide selected from the group consisting of human angiostatin, murine angiostatin, human endostatin, murine endostatin, and angiogenesis-inhibiting fragments thereof in the preparation of a medicament for inhibiting tumor growth in a human patient harboring a solid tumor, wherein expression of the anti-angiogenic polypeptide in the patient inhibits angiogenesis in the vicinity of the tumor and/or systemically by diffusion of the recombinant protein to the vascular compartment from secreting transduced cells, thereby inhibiting its growth.

2. Use of a nucleic acid molecule which expresses an anti-angiogenic polypeptide of the formula A-B, wherein

A and B are polypeptide and/or export signal joined by a polypeptide and/or export signal bond;

A contains at least amino acids and comprises kringles 1, 2, and 3 of human or murine angiostatin; and

B contains at least amino acids and includes at least 75% of the amino acid sequence of human or murine endostatin in the preparation of a medicament for inhibiting tumor growth in a human patient harboring a solid tumor, wherein expression of the anti-angiogenic polypeptide in the patient inhibits angiogenesis in the vicinity of the tumor and/or systemically by diffusion of the recombinant protein to the vascular compartment from secreting transduced cells, thereby inhibiting its growth.

3. The use of claim 2, wherein A further comprises kringle region 4 of

human or murine angiostatin.

4. The use of claim 2 or claim 3, wherein A further comprises kringle 5 of human or murine plasminogen.

5. The use of claim 1 or claim 2, wherein said nucleic acid molecule constitutes a portion of a viral vector.

6. The use of claim 1 or claim 2, wherein said nucleic acid molecule constitutesa portion of a plasmid.

7. The use of claim 6, wherein said plasmid is carried in a cell-free carrier so that the plasmid transfects living cells of the patient following plasmid administration, causing expression of the anti-angiogenesis polypeptide and/or export signal in the patient such that angiogenesis in the vicinity of the tumor and/or systemically by diffusion of the recombinant protein to the vascular compartment from secreting transduced cells is inhibited, causing inhibition of tumor growth.

8. The use of claim 6, wherein said plasmid has been transfected into animal cells *ex vivo*, wherein said animal cells express the anti-angiogenesis polypeptide to inhibit tumor-associated angiogenesis and tumor growth.

9. The use of claim 5, wherein said viral vector is carried in a cell-free carrier, so that the viral vector is incorporated into living cells of the patient following viral vector administration, causing expression of the anti-

angiogenesis polypeptide in the patient such that angiogenesis in the vicinity of the tumor and/or systemically by diffusion of the recombinant protein to the vascular compartment from secreting transduced cells is inhibited, causing inhibition of tumor growth.

10. The use of claim 5, wherein animal cells are infected with said viral vector *ex vivo* and then administered to said patient, wherein said animal cells express the anti-angiogenesis polypeptide to inhibit tumor-associated angiogenesis and tumor growth.

11. The use of claim 8, wherein said animal cells are human cells.

12. The use of claim 11, wherein said human cells are autologous.

13. The use of claim 11, wherein said human cells are allogeneic.

14. The use of claim 10, wherein said animal cells are human cells.

15. The use of claim 14, wherein said human cells are autologous.

16. The use of claim 14, wherein said human cells are allogeneic.

17. The use of claim 5, wherein said viral vector is a retroviral vector.

18. The use of claim 5, wherein said viral vector is a non-retroviral vector selected from the group consisting of adenoviral, adeno-associated, herpes, Simliki Forest virus, and poxvirus vectors.

19. The use of claim 17, wherein said retroviral vector is Murine Stem Cell Virus or a lentivirus.

20. The use of claim 1, wherein said angiostatin comprises kringles 1, 2 and 3.

21. The use of claim 20, wherein said angiostatin further comprises kringle 4.

22. The use of claim 1, wherein said anti-angiogenic polypeptide is a fusion of angiostatin or a biologically active fragment thereof and endostatin or a biologically active fragment thereof.

23. The use of claim 1, wherein said nucleic acid molecule includes a nucleotide sequence encoding a signal polypeptide and/or export signal for effecting secretion of said anti-angiogenesis polypeptide.

24. The use of claim 23, wherein said signal polypeptide and/or export signal is plasminogen signal polypeptide and/or export signal.

25. The use of claim 1, wherein said nucleic acid molecule includes a nucleotide sequence encoding a preactivation polypeptide and/or export signal for effecting Golgi and/or ER export of the anti-angiogenic polypeptide..

26. The use of claim 25, wherein said preactivation polypeptide and/or export signal is a preactivation polypeptide and/or export signal of a human protein of the blood coagulation cascade.

27. The use of claim 26, wherein said preactivation polypeptide and/or export signal is human plasminogen preactivation polypeptide and/or export signal.

28. The method of claim 25, wherein the preactivation encoding sequence is positioned between a signal-encoding sequence and the sequence encoding the anti-angiogenic polypeptide and/or export signal.

29. The use of claim 1, wherein said nucleic acid molecule includes a nucleotide sequence encoding a tag for identification of said anti-angiogenic polypeptide.

30. The method of claim 27, wherein said tag is a Flag tag polypeptide and/or export signal.

31. A viral gene therapy vector comprising a nucleic acid molecule which encodes an anti-angiogenic polypeptide selected from the group consisting of human angiostatin, murine angiostatin, human endostatin, murine endostatin, and angiogenesis-inhibiting fusions and fragments thereof, wherein said viral vector is sufficiently attenuated for use in human gene therapy.

32. A human cell infected with the vector of claim 31.

33. Use of a nucleic acid molecule which expresses in said patient an anti-angiogenic polypeptide selected from the group consisting of human angiostatin, murine angiostatin, human endostatin, murine endostatin, and angiogenesis-inhibiting fusions and fragments thereof, in the preparation of a

medicament for treating a human patient suffering from diabetic retinopathy, wherein expression of the anti-angiogenic polypeptide in the patient inhibits angiogenesis in the vicinity of the retina.

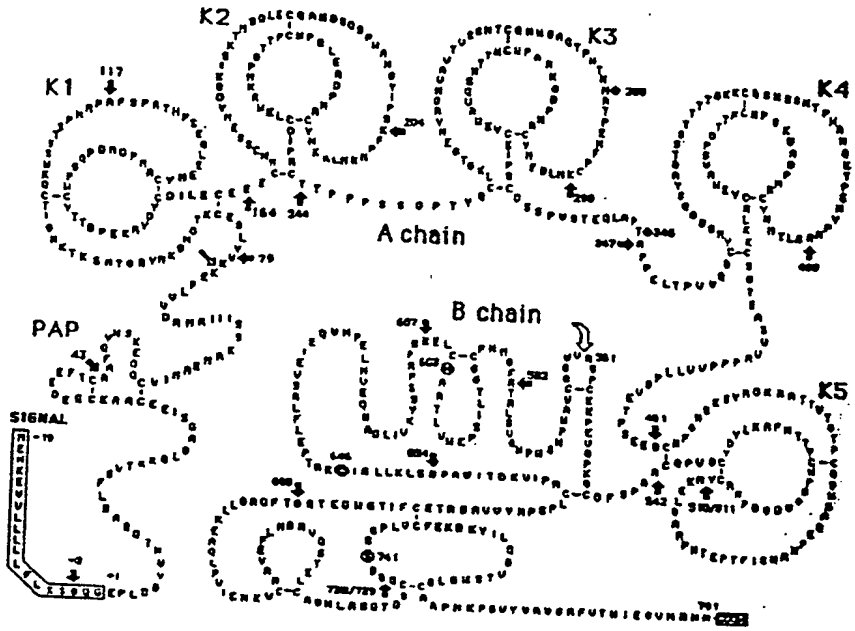
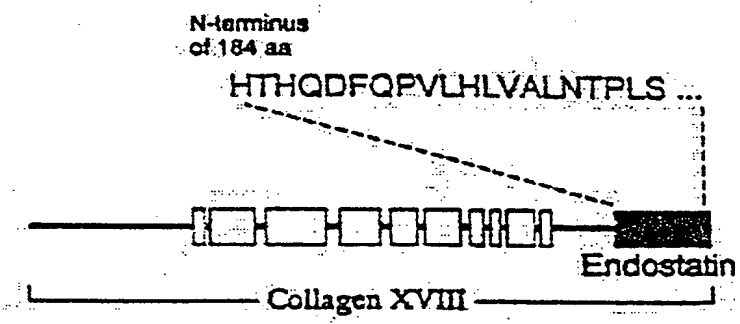


FIG. 1


N-terminus
of 184 aa
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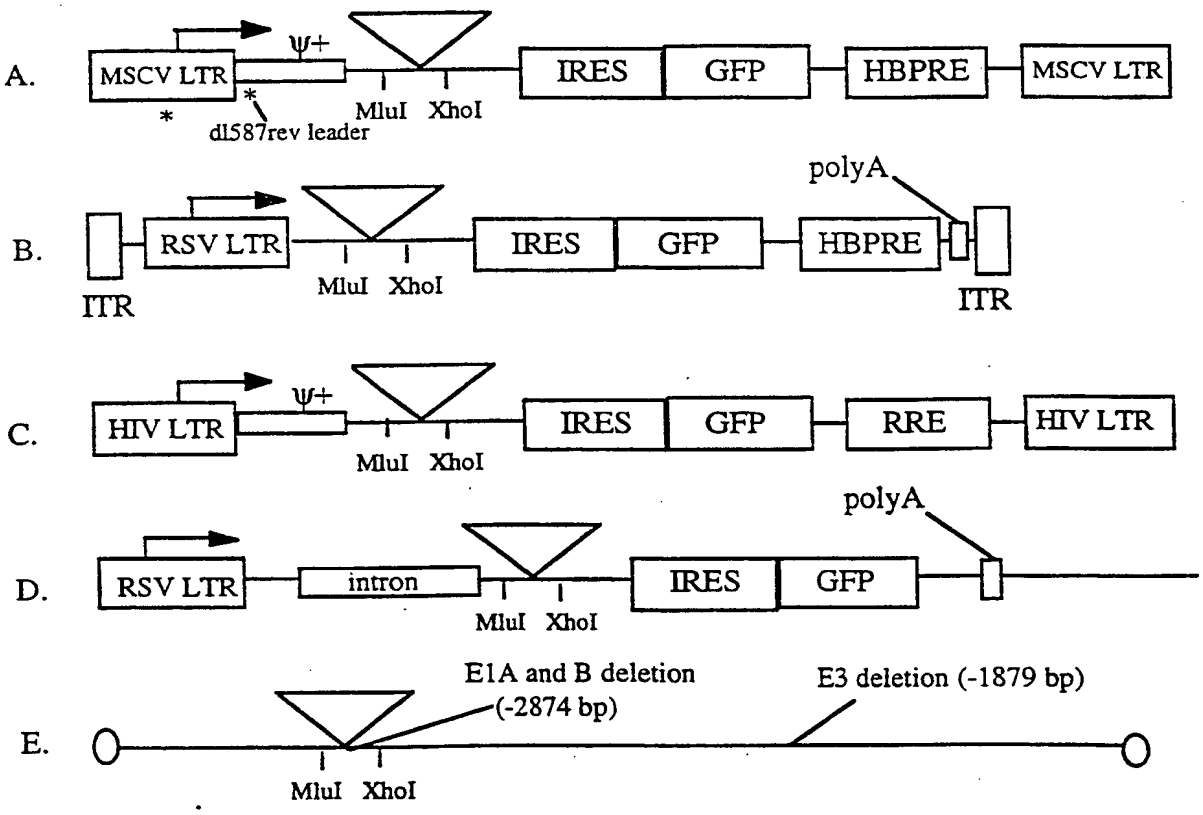
Endostatin
Collagen XVIII

Fig. 2


A.
MSCV LTR
ψ+
*
*
dl587rev leader
MluI XhoI
IRES
GFP
HBPRE
MSCV LTR
B.
polyA
RSV LTR
MluI XhoI
IRES
GFP
HBPRE
ITR
ITR
C.
HIV LTR
ψ+
MluI XhoI
IRES
GFP
RRE
HIV LTR
D.
polyA
RSV LTR
intron
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GFP
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FIG. 3

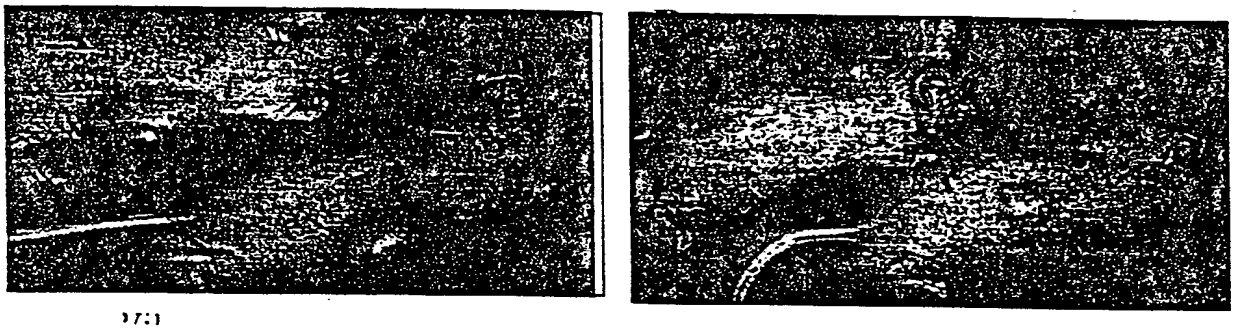


FIG. 4

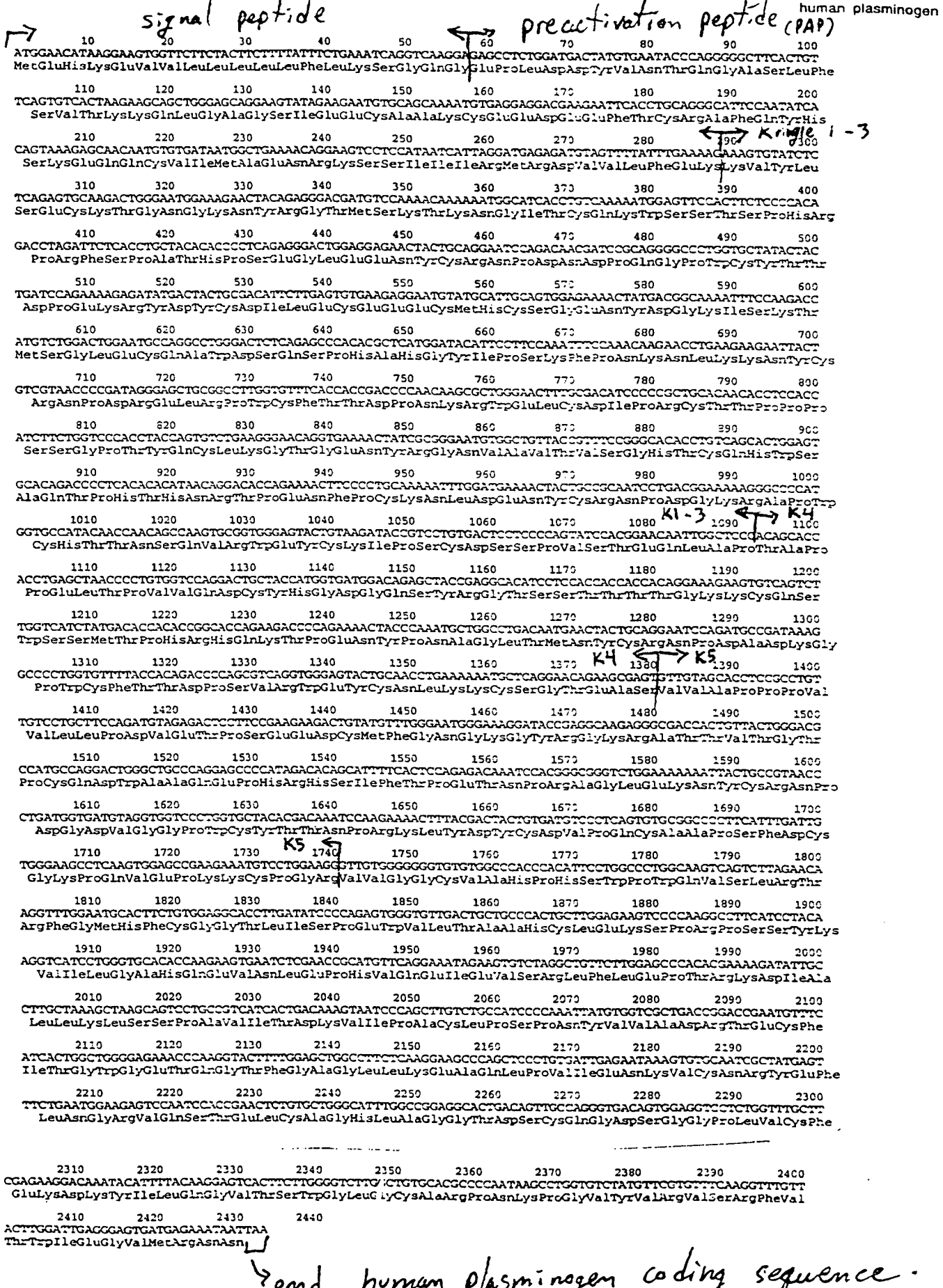

signal peptide
activation peptide (PAP)
human plasminogen
Kringle 1-3
K1-3
K4
K5
end human plasminogen coding sequence.

Fig. 5

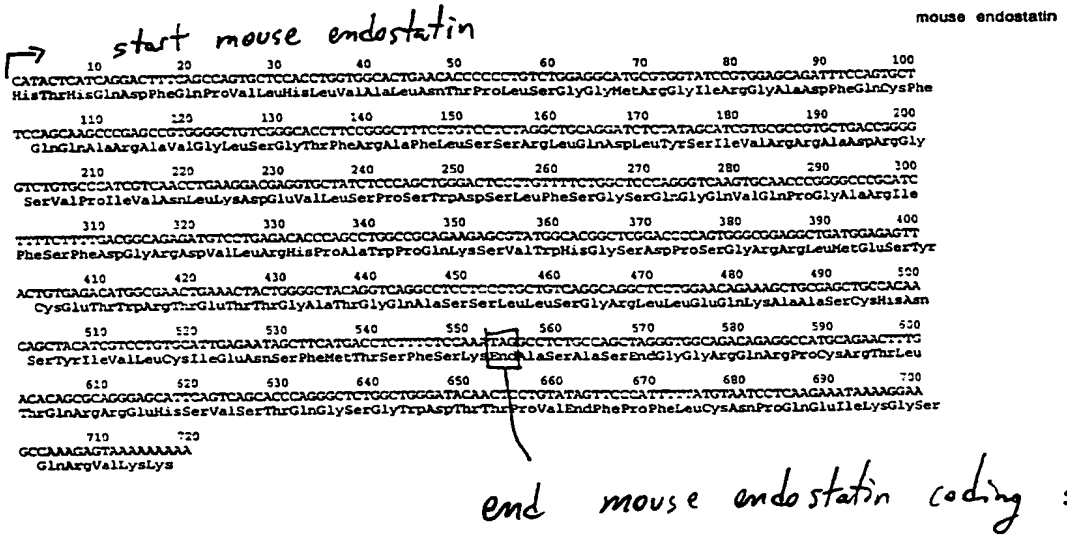
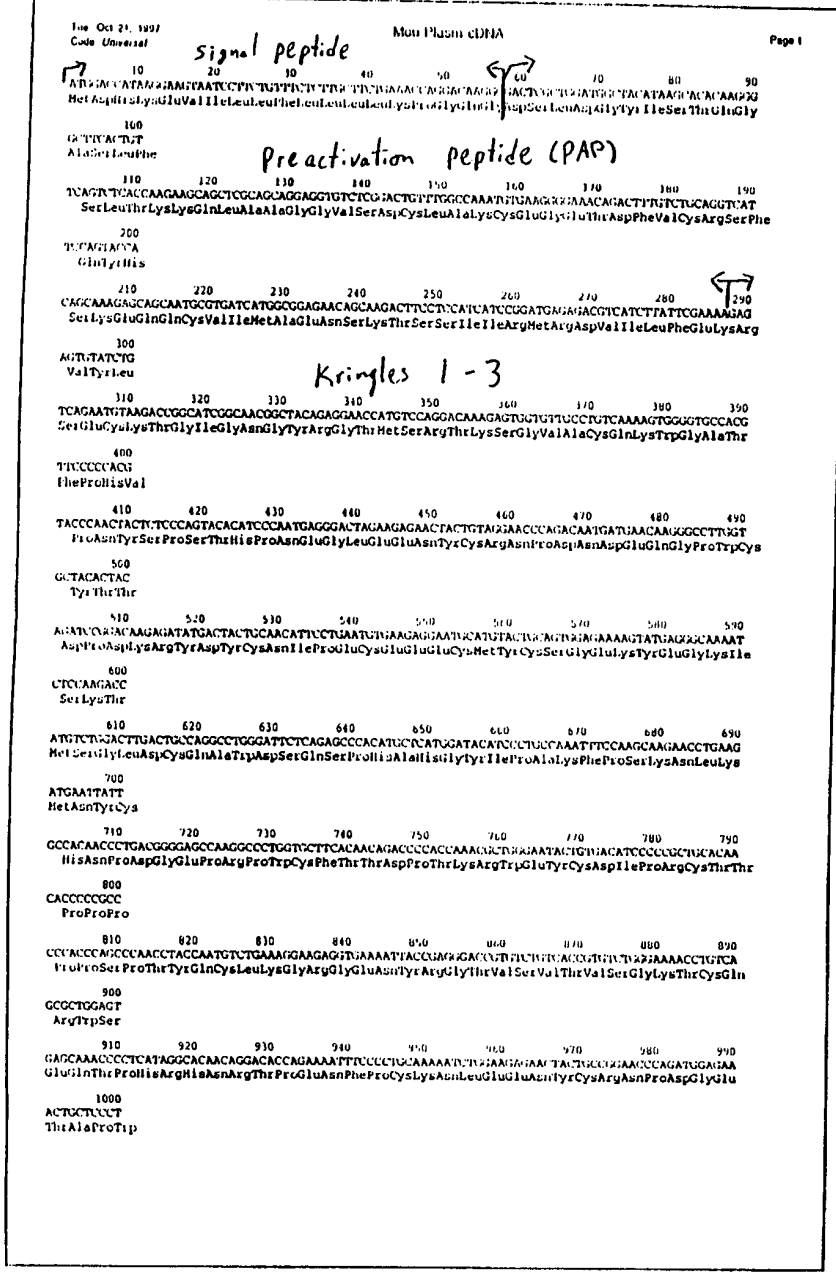

mouse endostatin
start mouse endostatin
end mouse endostatin coding sequence

Fig 6

Mouse Plasminogen cDNA



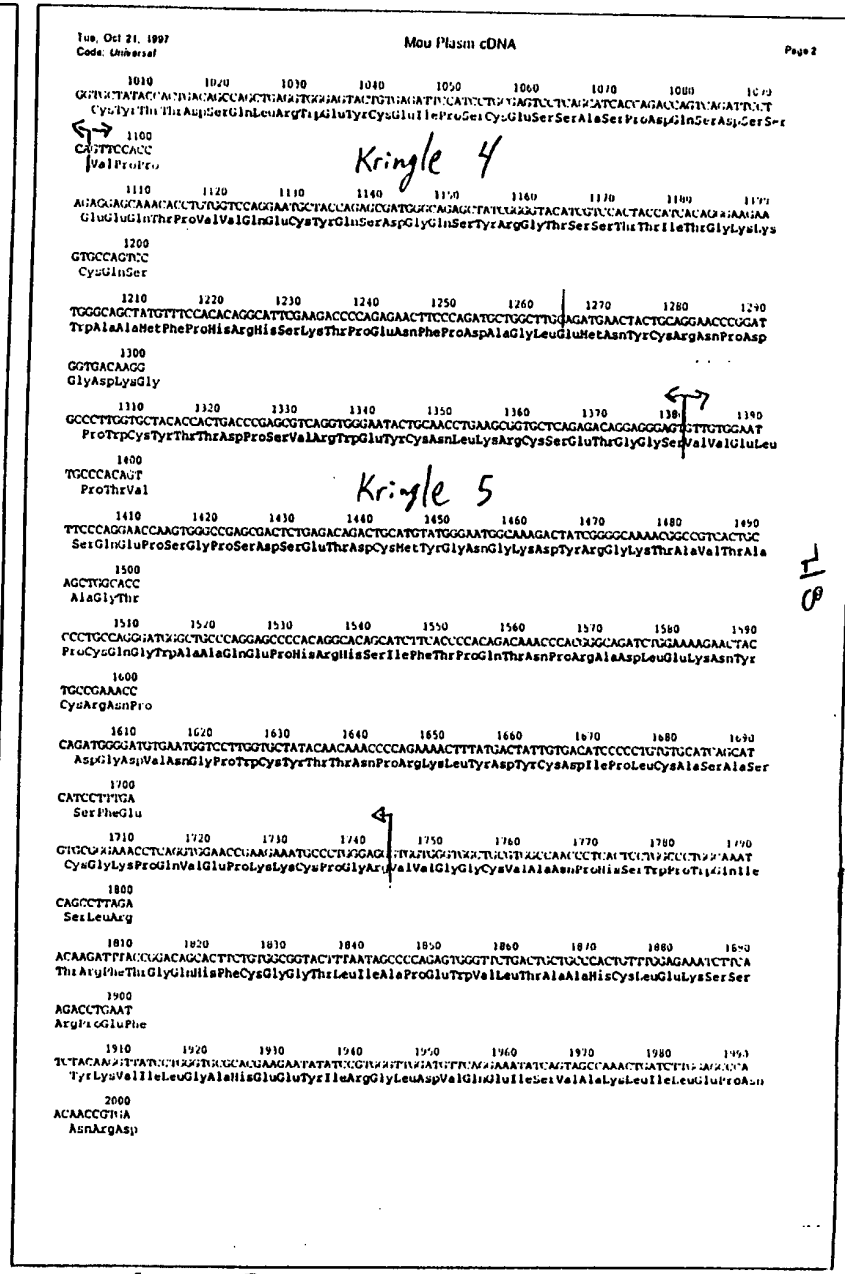


FIG. 7 (Sheet 1 of 2)

Tue, Oct 21, 1997 Mou Plasm cDNA Page 3
Code: *Universal*

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      2100
CCGGACAATA
 ArgThrIle

      2110       2120       2130       2140       2150       2160       2170       2180       2190
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      2200
TGCAACCGCG
CysAsnArgVal

      2210       2220       2230       2240       2250       2260       2270       2280       2290
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      2300
GACCTCTGGT
  ProLeuVal

      2310       2320       2330       2340       2350       2360       2370       2380       2390
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 CysPheGluLysAspLysTyrIleLeuGlnGlyValThrSerTrpGlyLeuGlyCysAlaArgProAsnLysProGlyValTyrValArg

      2400
TGTCTCACGG                    end plasminogen coding sequence.
 ValSerArg

      2410       2420       2430       2440       2450       2460       2470       2480       2490
TTTGTTGATTGGATTGAAAGGGAGATGAGGAATAACTGACTAGGTGGAAGGCCGAGCAAAACCTCTGCTTACTAAAGCTTACTGAATATG
PheValAspTrpIleGluArgGluMetArgAsnAsnEndLeuGlyGlyArgProSerLysThrSerAlaTyrEndSerLeuLeuAsnMet

      2500
GGGAGAGGGC
GlyArgGlyLeu

      2510       2520       2530       2540       2550       2560       2570       2580       2590
TTAGGGTGTTTGGAAAAACTGACAGTAATCAAACTGGGACACTACACTGAACCACAGCTTCCTGTCGCCCCTCAGCCCCTCCCCTTTTTT
  ArgValPheGlyLysThrAspSerAsnGlnThrGlyThrLeuHisEndThrThrAlaSerCysArgProSerAlaProProLeuPheLeu

      2600
TGTATTATTG
  TyrTyrCys

      2610       2620       2630       2640       2650       2660       2670       2680       2690
TGGGTAAAATTTTCCTGTCTGTGGACTTCTGGATTTTGTGACAATAGACCATCACTGCTGTGACCTTTGTTGAAAATAAACTCGATACTT
 GlyEndAsnPheProValCysGlyLeuLeuAspPheValThrIleAspHisHisCysCysAspLeuCysEndLysEndThrArgTyrLeu

      2700
ACTTTG
 Leu
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FIG. 7 (Sheet 2 of 2

SEQUENCE LISTING

<110> Genetix Pharmaceuticals, Inc.

<120> ANTI-ANGIOGENIC GENE THERAPY VECTORS AND THEIR USE IN TREATING ANGIOGENISIS-RELATED DISEASES

<130> 50033/002WO1

<140> PCT/US98/xxxxx
<141> 1998-11-20

<150> 08/975,424
<151> 1997-11-20

<160> 20

<170> FastSEQ for Windows Version 3.0

<210> 1
<211> 2433
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<213> Homo sapiens

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<221> CDS
<222> (1)...(2433)

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Met Glu His Lys Glu Val Val Leu Leu Leu Leu Leu Phe Leu Lys Ser
 1               5                  10                  15

ggt caa gga gag cct ctg gat gac tat gtg aat acc cag ggg gct tca        96
Gly Gln Gly Glu Pro Leu Asp Asp Tyr Val Asn Thr Gln Gly Ala Ser
             20                  25                  30

ctg ttc agt gtc act aag aag cag ctg gga gca gga agt ata gaa gaa       144
Leu Phe Ser Val Thr Lys Lys Gln Leu Gly Ala Gly Ser Ile Glu Glu
         35                  40                  45

tgt gca gca aaa tgt gag gag gac gaa gaa ttc acc tgc agg gca ttc       192
Cys Ala Ala Lys Cys Glu Glu Asp Glu Glu Phe Thr Cys Arg Ala Phe
     50                  55                  60

caa tat cac agt aaa gag caa caa tgt gtg ata atg gct gaa aac agg       240
Gln Tyr His Ser Lys Glu Gln Gln Cys Val Ile Met Ala Glu Asn Arg
 65                  70                  75                  80

aag tcc tcc ata atc att agg atg aga gat gta gtt tta ttt gaa aag       288
Lys Ser Ser Ile Ile Ile Arg Met Arg Asp Val Val Leu Phe Glu Lys
                 85                  90                  95
```

```
aaa gtg tat ctc tca gag tgc aag act ggg aat gga aag aac tac aga      336
Lys Val Tyr Leu Ser Glu Cys Lys Thr Gly Asn Gly Lys Asn Tyr Arg
            100                 105                 110

ggg acg atg tcc aaa aca aaa aat ggc atc acc tgt caa aaa tgg agt      384
Gly Thr Met Ser Lys Thr Lys Asn Gly Ile Thr Cys Gln Lys Trp Ser
        115                 120                 125

tcc act tct ccc cac aga cct aga ttc tca cct gct aca cac ccc tca      432
Ser Thr Ser Pro His Arg Pro Arg Phe Ser Pro Ala Thr His Pro Ser
    130                 135                 140

gag gga ctg gag gag aac tac tgc agg aat cca gac aac gat ccg cag      480
Glu Gly Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Pro Gln
145                 150                 155                 160

ggg ccc tgg tgc tat act act gat cca gaa aag aga tat gac tac tgc      528
Gly Pro Trp Cys Tyr Thr Thr Asp Pro Glu Lys Arg Tyr Asp Tyr Cys
                165                 170                 175

gac att ctt gag tgt gaa gag gaa tgt atg cat tgc agt gga gaa aac      576
Asp Ile Leu Glu Cys Glu Glu Glu Cys Met His Cys Ser Gly Glu Asn
            180                 185                 190

tat gac ggc aaa att tcc aag acc atg tct gga ctg gaa tgc cag gcc      624
Tyr Asp Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Glu Cys Gln Ala
        195                 200                 205

tgg gac tct cag agc cca cac gct cat gga tac att cct tcc aaa ttt      672
Trp Asp Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ser Lys Phe
    210                 215                 220

cca aac aag aac ctg aag aag aat tac tgt cgt aac ccc gat agg gag      720
Pro Asn Lys Asn Leu Lys Lys Asn Tyr Cys Arg Asn Pro Asp Arg Glu
225                 230                 235                 240

ctg cgg cct tgg tgt ttc acc acc gac ccc aac aag cgc tgg gaa ctt      768
Leu Arg Pro Trp Cys Phe Thr Thr Asp Pro Asn Lys Arg Trp Glu Leu
                245                 250                 255

tgc gac atc ccc cgc tgc aca aca cct cca cca tct tct ggt ccc acc      816
Cys Asp Ile Pro Arg Cys Thr Thr Pro Pro Pro Ser Ser Gly Pro Thr
            260                 265                 270

tac cag tgt ctg aag gga aca ggt gaa aac tat cgc ggg aat gtg gct      864
Tyr Gln Cys Leu Lys Gly Thr Gly Glu Asn Tyr Arg Gly Asn Val Ala
        275                 280                 285

gtt acc gtt tcc ggg cac acc tgt cag cac tgg agt gca cag acc cct      912
Val Thr Val Ser Gly His Thr Cys Gln His Trp Ser Ala Gln Thr Pro
    290                 295                 300

cac aca cat aac agg aca cca gaa aac ttc ccc tgc aaa aat ttg gat      960
His Thr His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Asp
305                 310                 315                 320
```

```
gaa aac tac tgc cgc aat cct gac gga aaa agg gcc cca tgg tgc cat      1008
Glu Asn Tyr Cys Arg Asn Pro Asp Gly Lys Arg Ala Pro Trp Cys His
                325                 330                 335

aca acc aac agc caa gtg cgg tgg gag tac tgt aag ata ccg tcc tgt      1056
Thr Thr Asn Ser Gln Val Arg Trp Glu Tyr Cys Lys Ile Pro Ser Cys
            340                 345                 350

gac tcc tcc cca gta tcc acg gaa caa ttg gct ccc aca gca cca cct      1104
Asp Ser Ser Pro Val Ser Thr Glu Gln Leu Ala Pro Thr Ala Pro Pro
        355                 360                 365

gag cta acc cct gtg gtc cag gac tgc tac cat ggt gat gga cag agc      1152
Glu Leu Thr Pro Val Val Gln Asp Cys Tyr His Gly Asp Gly Gln Ser
    370                 375                 380

tac cga ggc aca tcc tcc acc acc acc aca gga aag aag tgt cag tct      1200
Tyr Arg Gly Thr Ser Ser Thr Thr Thr Thr Gly Lys Lys Cys Gln Ser
385                 390                 395                 400

tgg tca tct atg aca cca cac cgg cac cag aag acc cca gaa aac tac      1248
Trp Ser Ser Met Thr Pro His Arg His Gln Lys Thr Pro Glu Asn Tyr
                405                 410                 415

cca aat gct ggc ctg aca atg aac tac tgc agg aat cca gat gcc gat      1296
Pro Asn Ala Gly Leu Thr Met Asn Tyr Cys Arg Asn Pro Asp Ala Asp
            420                 425                 430

aaa ggc ccc tgg tgt ttt acc aca gac ccc agc gtc agg tgg gag tac      1344
Lys Gly Pro Trp Cys Phe Thr Thr Asp Pro Ser Val Arg Trp Glu Tyr
        435                 440                 445

tgc aac ctg aaa aaa tgc tca gga aca gaa gcg agt gtt gta gca cct      1392
Cys Asn Leu Lys Lys Cys Ser Gly Thr Glu Ala Ser Val Val Ala Pro
    450                 455                 460

ccg cct gtt gtc ctg ctt cca gat gta gag act cct tcc gaa gaa gac      1440
Pro Pro Val Val Leu Leu Pro Asp Val Glu Thr Pro Ser Glu Glu Asp
465                 470                 475                 480

tgt atg ttt ggg aat ggg aaa gga tac cga ggc aag agg gcg acc act      1488
Cys Met Phe Gly Asn Gly Lys Gly Tyr Arg Gly Lys Arg Ala Thr Thr
                485                 490                 495

gtt act ggg acg cca tgc cag gac tgg gct gcc cag gag ccc cat aga      1536
Val Thr Gly Thr Pro Cys Gln Asp Trp Ala Ala Gln Glu Pro His Arg
            500                 505                 510

cac agc att ttc act cca gag aca aat cca cgg gcg ggt ctg gaa aaa      1584
His Ser Ile Phe Thr Pro Glu Thr Asn Pro Arg Ala Gly Leu Glu Lys
        515                 520                 525

aat tac tgc cgt aac cct gat ggt gat gta ggt ggt ccc tgg tgc tac      1632
Asn Tyr Cys Arg Asn Pro Asp Gly Asp Val Gly Gly Pro Trp Cys Tyr
```

```
    530                 535                 540

acg aca aat cca aga aaa ctt tac gac tac tgt gat gtc cct cag tgt     1680
Thr Thr Asn Pro Arg Lys Leu Tyr Asp Tyr Cys Asp Val Pro Gln Cys
545                 550                 555                 560

gcg gcc cct tca ttt gat tgt ggg aag cct caa gtg gag ccg aag aaa     1728
Ala Ala Pro Ser Phe Asp Cys Gly Lys Pro Gln Val Glu Pro Lys Lys
                565                 570                 575

tgt cct gga agg gtt gtg ggg ggg tgt gtg gcc cac cca cat tcc tgg     1776
Cys Pro Gly Arg Val Val Gly Gly Cys Val Ala His Pro His Ser Trp
            580                 585                 590

ccc tgg caa gtc agt ctt aga aca agg ttt gga atg cac ttc tgt gga     1824
Pro Trp Gln Val Ser Leu Arg Thr Arg Phe Gly Met His Phe Cys Gly
        595                 600                 605

ggc acc ttg ata tcc cca gag tgg gtg ttg act gct gcc cac tgc ttg     1872
Gly Thr Leu Ile Ser Pro Glu Trp Val Leu Thr Ala Ala His Cys Leu
    610                 615                 620

gag aag tcc cca agg cct tca tcc tac aag gtc atc ctg ggt gca cac     1920
Glu Lys Ser Pro Arg Pro Ser Ser Tyr Lys Val Ile Leu Gly Ala His
625                 630                 635                 640

caa gaa gtg aat ctc gaa ccg cat gtt cag gaa ata gaa gtg tct agg     1968
Gln Glu Val Asn Leu Glu Pro His Val Gln Glu Ile Glu Val Ser Arg
                645                 650                 655

ctg ttc ttg gag ccc aca cga aaa gat att gcc ttg cta aag cta agc     2016
Leu Phe Leu Glu Pro Thr Arg Lys Asp Ile Ala Leu Leu Lys Leu Ser
            660                 665                 670

agt cct gcc gtc atc act gac aaa gta atc cca gct tgt ctg cca tcc     2064
Ser Pro Ala Val Ile Thr Asp Lys Val Ile Pro Ala Cys Leu Pro Ser
        675                 680                 685

cca aat tat gtg gtc gct gac cgg acc gaa tgt ttc atc act ggc tgg     2112
Pro Asn Tyr Val Val Ala Asp Arg Thr Glu Cys Phe Ile Thr Gly Trp
    690                 695                 700

gga gaa acc caa ggt act ttt gga gct ggc ctt ctc aag gaa gcc cag     2160
Gly Glu Thr Gln Gly Thr Phe Gly Ala Gly Leu Leu Lys Glu Ala Gln
705                 710                 715                 720

ctc cct gtg att gag aat aaa gtg tgc aat cgc tat gag ttt ctg aat     2208
Leu Pro Val Ile Glu Asn Lys Val Cys Asn Arg Tyr Glu Phe Leu Asn
                725                 730                 735

gga aga gtc caa tcc acc gaa ctc tgt gct ggg cat ttg gcc gga ggc     2256
Gly Arg Val Gln Ser Thr Glu Leu Cys Ala Gly His Leu Ala Gly Gly
            740                 745                 750

act gac agt tgc cag ggt gac agt gga ggt cct ctg gtt tgc ttc gag     2304
```

```
Thr Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Phe Glu
        755                 760                 765

aag gac aaa tac att tta caa gga gtc act tct tgg ggt ctt ggc tgt     2352
Lys Asp Lys Tyr Ile Leu Gln Gly Val Thr Ser Trp Gly Leu Gly Cys
    770                 775                 780

gca cgc ccc aat aag cct ggt gtc tat gtt cgt gtt tca agg ttt gtt     2400
Ala Arg Pro Asn Lys Pro Gly Val Tyr Val Arg Val Ser Arg Phe Val
785                 790                 795                 800

act tgg att gag gga gtg atg aga aat aat taa                        2433
Thr Trp Ile Glu Gly Val Met Arg Asn Asn  *
                805                 810
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<212> PRT
<213> Homo sapiens

<400> 2

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 1               5                  10                  15
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            20                  25                  30
Leu Phe Ser Val Thr Lys Lys Gln Leu Gly Ala Gly Ser Ile Glu Glu
        35                  40                  45
Cys Ala Ala Lys Cys Glu Glu Asp Glu Glu Phe Thr Cys Arg Ala Phe
    50                  55                  60
Gln Tyr His Ser Lys Glu Gln Gln Cys Val Ile Met Ala Glu Asn Arg
65                  70                  75                  80
Lys Ser Ser Ile Ile Ile Arg Met Arg Asp Val Val Leu Phe Glu Lys
                85                  90                  95
Lys Val Tyr Leu Ser Glu Cys Lys Thr Gly Asn Gly Lys Asn Tyr Arg
            100                 105                 110
Gly Thr Met Ser Lys Thr Lys Asn Gly Ile Thr Cys Gln Lys Trp Ser
        115                 120                 125
Ser Thr Ser Pro His Arg Pro Arg Phe Ser Pro Ala Thr His Pro Ser
    130                 135                 140
Glu Gly Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Pro Gln
145                 150                 155                 160
Gly Pro Trp Cys Tyr Thr Thr Asp Pro Glu Lys Arg Tyr Asp Tyr Cys
                165                 170                 175
Asp Ile Leu Glu Cys Glu Glu Glu Cys Met His Cys Ser Gly Glu Asn
            180                 185                 190
Tyr Asp Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Glu Cys Gln Ala
        195                 200                 205
Trp Asp Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ser Lys Phe
    210                 215                 220
Pro Asn Lys Asn Leu Lys Lys Asn Tyr Cys Arg Asn Pro Asp Arg Glu
225                 230                 235                 240
Leu Arg Pro Trp Cys Phe Thr Thr Asp Pro Asn Lys Arg Trp Glu Leu
                245                 250                 255
Cys Asp Ile Pro Arg Cys Thr Thr Pro Pro Pro Ser Ser Gly Pro Thr
```

```
            260                 265                 270
Tyr Gln Cys Leu Lys Gly Thr Gly Glu Asn Tyr Arg Gly Asn Val Ala
        275                 280                 285
Val Thr Val Ser Gly His Thr Cys Gln His Trp Ser Ala Gln Thr Pro
    290                 295                 300
His Thr His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Asp
305                 310                 315                 320
Glu Asn Tyr Cys Arg Asn Pro Asp Gly Lys Arg Ala Pro Trp Cys His
                325                 330                 335
Thr Thr Asn Ser Gln Val Arg Trp Glu Tyr Cys Lys Ile Pro Ser Cys
            340                 345                 350
Asp Ser Ser Pro Val Ser Thr Glu Gln Leu Ala Pro Thr Ala Pro Pro
        355                 360                 365
Glu Leu Thr Pro Val Val Gln Asp Cys Tyr His Gly Asp Gly Gln Ser
    370                 375                 380
Tyr Arg Gly Thr Ser Ser Thr Thr Thr Thr Gly Lys Lys Cys Gln Ser
385                 390                 395                 400
Trp Ser Ser Met Thr Pro His Arg His Gln Lys Thr Pro Glu Asn Tyr
                405                 410                 415
Pro Asn Ala Gly Leu Thr Met Asn Tyr Cys Arg Asn Pro Asp Ala Asp
            420                 425                 430
Lys Gly Pro Trp Cys Phe Thr Thr Asp Pro Ser Val Arg Trp Glu Tyr
        435                 440                 445
Cys Asn Leu Lys Lys Cys Ser Gly Thr Glu Ala Ser Val Val Ala Pro
    450                 455                 460
Pro Pro Val Val Leu Leu Pro Asp Val Glu Thr Pro Ser Glu Glu Asp
465                 470                 475                 480
Cys Met Phe Gly Asn Gly Lys Gly Tyr Arg Gly Lys Arg Ala Thr Thr
                485                 490                 495
Val Thr Gly Thr Pro Cys Gln Asp Trp Ala Ala Gln Glu Pro His Arg
            500                 505                 510
His Ser Ile Phe Thr Pro Glu Thr Asn Pro Arg Ala Gly Leu Glu Lys
        515                 520                 525
Asn Tyr Cys Arg Asn Pro Asp Gly Asp Val Gly Gly Pro Trp Cys Tyr
    530                 535                 540
Thr Thr Asn Pro Arg Lys Leu Tyr Asp Tyr Cys Asp Val Pro Gln Cys
545                 550                 555                 560
Ala Ala Pro Ser Phe Asp Cys Gly Lys Pro Gln Val Glu Pro Lys Lys
                565                 570                 575
Cys Pro Gly Arg Val Val Gly Gly Cys Val Ala His Pro His Ser Trp
            580                 585                 590
Pro Trp Gln Val Ser Leu Arg Thr Arg Phe Gly Met His Phe Cys Gly
        595                 600                 605
Gly Thr Leu Ile Ser Pro Glu Trp Val Leu Thr Ala Ala His Cys Leu
    610                 615                 620
Glu Lys Ser Pro Arg Pro Ser Ser Tyr Lys Val Ile Leu Gly Ala His
625                 630                 635                 640
Gln Glu Val Asn Leu Glu Pro His Val Gln Glu Ile Glu Val Ser Arg
                645                 650                 655
Leu Phe Leu Glu Pro Thr Arg Lys Asp Ile Ala Leu Leu Lys Leu Ser
            660                 665                 670
Ser Pro Ala Val Ile Thr Asp Lys Val Ile Pro Ala Cys Leu Pro Ser
        675                 680                 685
Pro Asn Tyr Val Val Ala Asp Arg Thr Glu Cys Phe Ile Thr Gly Trp
    690                 695                 700
```

```
Gly Glu Thr Gln Gly Thr Phe Gly Ala Gly Leu Leu Lys Glu Ala Gln
705                 710                 715                 720
Leu Pro Val Ile Glu Asn Lys Val Cys Asn Arg Tyr Glu Phe Leu Asn
                725                 730                 735
Gly Arg Val Gln Ser Thr Glu Leu Cys Ala Gly His Leu Ala Gly Gly
            740                 745                 750
Thr Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Phe Glu
        755                 760                 765
Lys Asp Lys Tyr Ile Leu Gln Gly Val Thr Ser Trp Gly Leu Gly Cys
    770                 775                 780
Ala Arg Pro Asn Lys Pro Gly Val Tyr Val Arg Val Ser Arg Phe Val
785                 790                 795                 800
Thr Trp Ile Glu Gly Val Met Arg Asn Asn
                805                 810
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<222> (1)...(2436)

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Met Asp His Lys Glu Val Ile Leu Leu Phe Leu Leu Leu Leu Lys Pro
 1               5                  10                  15

gga caa ggg gac tcg ctg gat ggc tac ata agc aca caa ggg gct tca        96
Gly Gln Gly Asp Ser Leu Asp Gly Tyr Ile Ser Thr Gln Gly Ala Ser
             20                  25                  30

ctg ttc agt ctc acc aag aag cag ctc gca gca gga ggt gtc tcg gac       144
Leu Phe Ser Leu Thr Lys Lys Gln Leu Ala Ala Gly Gly Val Ser Asp
         35                  40                  45

tgt ttg gcc aaa tgt gaa ggg gaa aca gac ttt gtc tgc agg tca ttc       192
Cys Leu Ala Lys Cys Glu Gly Glu Thr Asp Phe Val Cys Arg Ser Phe
     50                  55                  60

cag tac cac agc aaa gag cag caa tgc gtg atc atg gcg gag aac agc       240
Gln Tyr His Ser Lys Glu Gln Gln Cys Val Ile Met Ala Glu Asn Ser
 65                  70                  75                  80

aag act tcc tcc atc atc cgg atg aga gac gtc atc tta ttc gaa aag       288
Lys Thr Ser Ser Ile Ile Arg Met Arg Asp Val Ile Leu Phe Glu Lys
                 85                  90                  95

aga gtg tat ctg tca gaa tgt aag acc ggc atc ggc aac ggc tac aga       336
Arg Val Tyr Leu Ser Glu Cys Lys Thr Gly Ile Gly Asn Gly Tyr Arg
             100                 105                 110

gga acc atg tcc agg aca aag agt ggt gtt gcc tgt caa aag tgg ggt       384
Gly Thr Met Ser Arg Thr Lys Ser Gly Val Ala Cys Gln Lys Trp Gly
```

```
        115                 120                 125

gcc acg ttc ccc cac gta ccc aac tac tct ccc agt aca cat ccc aat      432
Ala Thr Phe Pro His Val Pro Asn Tyr Ser Pro Ser Thr His Pro Asn
    130                 135                 140

gag gga cta gaa gag aac tac tgt agg aac cca gac aat gat gaa caa      480
Glu Gly Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Glu Gln
145                 150                 155                 160

ggg cct tgg tgc tac act aca gat ccg gac aag aga tat gac tac tgc      528
Gly Pro Trp Cys Tyr Thr Thr Asp Pro Asp Lys Arg Tyr Asp Tyr Cys
                165                 170                 175

aac att cct gaa tgt gaa gag gaa tgc atg tac tgc agt gga gaa aag      576
Asn Ile Pro Glu Cys Glu Glu Glu Cys Met Tyr Cys Ser Gly Glu Lys
            180                 185                 190

tat gag ggc aaa atc tcc aag acc atg tct gga ctt gac tgc cag gcc      624
Tyr Glu Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Asp Cys Gln Ala
        195                 200                 205

tgg gat tct cag agc cca cat gct cat gga tac atc cct gcc aaa ttt      672
Trp Asp Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ala Lys Phe
    210                 215                 220

cca agc aag aac ctg aag atg aat tat tgc cac aac cct gac ggg gag      720
Pro Ser Lys Asn Leu Lys Met Asn Tyr Cys His Asn Pro Asp Gly Glu
225                 230                 235                 240

cca agg ccc tgg tgc ttc aca aca gac ccc acc aaa cgc tgg gaa tac      768
Pro Arg Pro Trp Cys Phe Thr Thr Asp Pro Thr Lys Arg Trp Glu Tyr
                245                 250                 255

tgt gac atc ccc cgc tgc aca aca ccc ccg ccc cca ccc agc cca acc      816
Cys Asp Ile Pro Arg Cys Thr Thr Pro Pro Pro Pro Pro Ser Pro Thr
            260                 265                 270

tac caa tgt ctg aaa gga aga ggt gaa aat tac cga ggg acc gtg tct      864
Tyr Gln Cys Leu Lys Gly Arg Gly Glu Asn Tyr Arg Gly Thr Val Ser
        275                 280                 285

gtc acc gtg tct ggg aaa acc tgt cag cgc tgg agt gag caa acc cct      912
Val Thr Val Ser Gly Lys Thr Cys Gln Arg Trp Ser Glu Gln Thr Pro
    290                 295                 300

cat agg cac aac agg aca cca gaa aat ttc ccc tgc aaa aat ctg gaa      960
His Arg His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Glu
305                 310                 315                 320

gag aac tac tgc cgg aac cca gat gga gaa act gct ccc tgg tgc tat     1008
Glu Asn Tyr Cys Arg Asn Pro Asp Gly Glu Thr Ala Pro Trp Cys Tyr
                325                 330                 335

acc act gac agc cag ctg agg tgg gag tac tgt gag att cca tcc tgc     1056
```

```
Thr Thr Asp Ser Gln Leu Arg Trp Glu Tyr Cys Glu Ile Pro Ser Cys
            340                 345                 350

gag tcc tca gca tca cca gac cag tca gat tcc tca gtt cca cca gag     1104
Glu Ser Ser Ala Ser Pro Asp Gln Ser Asp Ser Ser Val Pro Pro Glu
        355                 360                 365

gag caa aca cct gtg gtc cag gaa tgc tac cag agc gat ggg cag agc     1152
Glu Gln Thr Pro Val Val Gln Glu Cys Tyr Gln Ser Asp Gly Gln Ser
    370                 375                 380

tat cgg ggt aca tcg tcc act acc atc aca ggg aag aag tgc cag tcc     1200
Tyr Arg Gly Thr Ser Ser Thr Thr Ile Thr Gly Lys Lys Cys Gln Ser
385                 390                 395                 400

tgg gca gct atg ttt cca cac agg cat tcg aag acc cca gag aac ttc     1248
Trp Ala Ala Met Phe Pro His Arg His Ser Lys Thr Pro Glu Asn Phe
                405                 410                 415

cca gat gct ggc ttg gag atg aac tac tgc agg aac ccg gat ggt gac     1296
Pro Asp Ala Gly Leu Glu Met Asn Tyr Cys Arg Asn Pro Asp Gly Asp
            420                 425                 430

aag ggc cct tgg tgc tac acc act gac ccg agc gtc agg tgg gaa tac     1344
Lys Gly Pro Trp Cys Tyr Thr Thr Asp Pro Ser Val Arg Trp Glu Tyr
        435                 440                 445

tgc aac ctg aag cgg tgc tca gag aca gga ggg agt gtt gtg gaa ttg     1392
Cys Asn Leu Lys Arg Cys Ser Glu Thr Gly Gly Ser Val Val Glu Leu
    450                 455                 460

ccc aca gtt tcc cag gaa cca agt ggg ccg agc gac tct gag aca gac     1440
Pro Thr Val Ser Gln Glu Pro Ser Gly Pro Ser Asp Ser Glu Thr Asp
465                 470                 475                 480

tgc atg tat ggg aat ggc aaa gac tat cgg ggc aaa acg gcc gtc act     1488
Cys Met Tyr Gly Asn Gly Lys Asp Tyr Arg Gly Lys Thr Ala Val Thr
                485                 490                 495

gca gct ggc acc ccc tgc cag gga tgg gct gcc cag gag ccc cac agg     1536
Ala Ala Gly Thr Pro Cys Gln Gly Trp Ala Ala Gln Glu Pro His Arg
            500                 505                 510

cac agc atc ttc acc cca cag aca aac cca cgg gca gat ctg gaa aag     1584
His Ser Ile Phe Thr Pro Gln Thr Asn Pro Arg Ala Asp Leu Glu Lys
        515                 520                 525

aac tac tgc cga aac cca gat ggg gat gtg aat ggt cct tgg tgc tat     1632
Asn Tyr Cys Arg Asn Pro Asp Gly Asp Val Asn Gly Pro Trp Cys Tyr
    530                 535                 540

aca aca aac ccc aga aaa ctt tat gac tat tgt gac atc ccc ctg tgt     1680
Thr Thr Asn Pro Arg Lys Leu Tyr Asp Tyr Cys Asp Ile Pro Leu Cys
545                 550                 555                 560
```

```
gca tca gca tca tcc ttt gag tgc ggg aaa cct cag gtg gaa ccg aag      1728
Ala Ser Ala Ser Ser Phe Glu Cys Gly Lys Pro Gln Val Glu Pro Lys
                565                 570                 575

aaa tgc cct ggg agg gtg gtg ggt ggc tgc gtg gcc aac cct cac tcc      1776
Lys Cys Pro Gly Arg Val Val Gly Gly Cys Val Ala Asn Pro His Ser
            580                 585                 590

tgg ccc tgg caa atc agc ctt aga aca aga ttt acc gga cag cac ttc      1824
Trp Pro Trp Gln Ile Ser Leu Arg Thr Arg Phe Thr Gly Gln His Phe
        595                 600                 605

tgt ggc ggt act tta ata gcc cca gag tgg gtt ctg act gct gcc cac      1872
Cys Gly Gly Thr Leu Ile Ala Pro Glu Trp Val Leu Thr Ala Ala His
    610                 615                 620

tgt ttg gag aaa tct tca aga cct gaa ttc tac aag gtt atc ctg ggt      1920
Cys Leu Glu Lys Ser Ser Arg Pro Glu Phe Tyr Lys Val Ile Leu Gly
625                 630                 635                 640

gcg cac gaa gaa tat atc cgt ggg ttg gat gtt cag gaa ata tca gta      1968
Ala His Glu Glu Tyr Ile Arg Gly Leu Asp Val Gln Glu Ile Ser Val
                645                 650                 655

gcc aaa ctg atc ttg gag ccc aac aac cgt gac att gcc ctg ctg aaa      2016
Ala Lys Leu Ile Leu Glu Pro Asn Asn Arg Asp Ile Ala Leu Leu Lys
            660                 665                 670

cta agc cgc cca gcc acc atc acg gat aaa gtc att cca gct tgt ctg      2064
Leu Ser Arg Pro Ala Thr Ile Thr Asp Lys Val Ile Pro Ala Cys Leu
        675                 680                 685

cca tct cca aat tac atg gtt gct gac cgg aca ata tgt tac atc acc      2112
Pro Ser Pro Asn Tyr Met Val Ala Asp Arg Thr Ile Cys Tyr Ile Thr
    690                 695                 700

ggc tgg gga gag act caa ggg act ttc ggt gcc ggt cgt ctc aag gag      2160
Gly Trp Gly Glu Thr Gln Gly Thr Phe Gly Ala Gly Arg Leu Lys Glu
705                 710                 715                 720

gct cag ctg cct gtg att gag aac aag gtg tgc aac cgc gtc gag tat      2208
Ala Gln Leu Pro Val Ile Glu Asn Lys Val Cys Asn Arg Val Glu Tyr
                725                 730                 735

ctg aac aac aga gtc aaa tcc acg gag ctc tgt gcc ggg caa ctg gct      2256
Leu Asn Asn Arg Val Lys Ser Thr Glu Leu Cys Ala Gly Gln Leu Ala
            740                 745                 750

ggt ggc gtc gac agc tgc caa ggc gac agt gga gga cct ctg gtt tgc      2304
Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys
        755                 760                 765

ttc gag aag gac aag tac att tta caa gga gtc act tct tgg ggt ctt      2352
Phe Glu Lys Asp Lys Tyr Ile Leu Gln Gly Val Thr Ser Trp Gly Leu
    770                 775                 780
```

```
ggc tgt gct cgc ccc aat aag cct ggt gtc tac gtt cgt gtc tca cgg     2400
Gly Cys Ala Arg Pro Asn Lys Pro Gly Val Tyr Val Arg Val Ser Arg
785                 790                 795                 800

ttt gtt gat tgg att gaa agg gag atg agg aat aac tgactaggtg         2446
Phe Val Asp Trp Ile Glu Arg Glu Met Arg Asn Asn
                805                 810

gaaggccgag caaaacctct gcttactaaa gcttactgaa tatggggaga gggcttaggg   2506
tgtttggaaa aactgacagt aatcaaactg ggacactaca ctgaaccaca gcttcctgtc   2566
gcccctcagc ccctcccctt tttttgtatt attgtgggta aaatttttcct gtctgtggac   2626
ttctggattt tgtgacaata gaccatcact gctgtgacct ttgttgaaaa taaactcgat   2686
acttactttg                                                          2696
```

<210> 4
<211> 812
<212> PRT
<213> Mus musculus

<400> 4

```
Met Asp His Lys Glu Val Ile Leu Leu Phe Leu Leu Leu Leu Lys Pro
 1               5                  10                  15
Gly Gln Gly Asp Ser Leu Asp Gly Tyr Ile Ser Thr Gln Gly Ala Ser
            20                  25                  30
Leu Phe Ser Leu Thr Lys Lys Gln Leu Ala Ala Gly Gly Val Ser Asp
        35                  40                  45
Cys Leu Ala Lys Cys Glu Gly Glu Thr Asp Phe Val Cys Arg Ser Phe
    50                  55                  60
Gln Tyr His Ser Lys Glu Gln Gln Cys Val Ile Met Ala Glu Asn Ser
65                  70                  75                  80
Lys Thr Ser Ser Ile Ile Arg Met Arg Asp Val Ile Leu Phe Glu Lys
                85                  90                  95
Arg Val Tyr Leu Ser Glu Cys Lys Thr Gly Ile Gly Asn Gly Tyr Arg
            100                 105                 110
Gly Thr Met Ser Arg Thr Lys Ser Gly Val Ala Cys Gln Lys Trp Gly
        115                 120                 125
Ala Thr Phe Pro His Val Pro Asn Tyr Ser Pro Ser Thr His Pro Asn
    130                 135                 140
Glu Gly Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Glu Gln
145                 150                 155                 160
Gly Pro Trp Cys Tyr Thr Thr Asp Pro Asp Lys Arg Tyr Asp Tyr Cys
                165                 170                 175
Asn Ile Pro Glu Cys Glu Glu Glu Cys Met Tyr Cys Ser Gly Glu Lys
            180                 185                 190
Tyr Glu Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Asp Cys Gln Ala
        195                 200                 205
Trp Asp Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ala Lys Phe
    210                 215                 220
Pro Ser Lys Asn Leu Lys Met Asn Tyr Cys His Asn Pro Asp Gly Glu
225                 230                 235                 240
Pro Arg Pro Trp Cys Phe Thr Thr Asp Pro Thr Lys Arg Trp Glu Tyr
                245                 250                 255
Cys Asp Ile Pro Arg Cys Thr Thr Pro Pro Pro Pro Pro Ser Pro Thr
            260                 265                 270
```

```
Tyr Gln Cys Leu Lys Gly Arg Gly Glu Asn Tyr Arg Gly Thr Val Ser
        275                 280                 285
Val Thr Val Ser Gly Lys Thr Cys Gln Arg Trp Ser Glu Gln Thr Pro
    290                 295                 300
His Arg His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Glu
305                 310                 315                 320
Glu Asn Tyr Cys Arg Asn Pro Asp Gly Glu Thr Ala Pro Trp Cys Tyr
                325                 330                 335
Thr Thr Asp Ser Gln Leu Arg Trp Glu Tyr Cys Glu Ile Pro Ser Cys
            340                 345                 350
Glu Ser Ser Ala Ser Pro Asp Gln Ser Asp Ser Ser Val Pro Pro Glu
        355                 360                 365
Glu Gln Thr Pro Val Val Gln Glu Cys Tyr Gln Ser Asp Gly Gln Ser
    370                 375                 380
Tyr Arg Gly Thr Ser Ser Thr Thr Ile Thr Gly Lys Lys Cys Gln Ser
385                 390                 395                 400
Trp Ala Ala Met Phe Pro His Arg His Ser Lys Thr Pro Glu Asn Phe
                405                 410                 415
Pro Asp Ala Gly Leu Glu Met Asn Tyr Cys Arg Asn Pro Asp Gly Asp
            420                 425                 430
Lys Gly Pro Trp Cys Tyr Thr Thr Asp Pro Ser Val Arg Trp Glu Tyr
        435                 440                 445
Cys Asn Leu Lys Arg Cys Ser Glu Thr Gly Gly Ser Val Val Glu Leu
    450                 455                 460
Pro Thr Val Ser Gln Glu Pro Ser Gly Pro Ser Asp Ser Glu Thr Asp
465                 470                 475                 480
Cys Met Tyr Gly Asn Gly Lys Asp Tyr Arg Gly Lys Thr Ala Val Thr
                485                 490                 495
Ala Ala Gly Thr Pro Cys Gln Gly Trp Ala Ala Gln Glu Pro His Arg
            500                 505                 510
His Ser Ile Phe Thr Pro Gln Thr Asn Pro Arg Ala Asp Leu Glu Lys
        515                 520                 525
Asn Tyr Cys Arg Asn Pro Asp Gly Asp Val Asn Gly Pro Trp Cys Tyr
    530                 535                 540
Thr Thr Asn Pro Arg Lys Leu Tyr Asp Tyr Cys Asp Ile Pro Leu Cys
545                 550                 555                 560
Ala Ser Ala Ser Ser Phe Glu Cys Gly Lys Pro Gln Val Glu Pro Lys
                565                 570                 575
Lys Cys Pro Gly Arg Val Val Gly Gly Cys Val Ala Asn Pro His Ser
            580                 585                 590
Trp Pro Trp Gln Ile Ser Leu Arg Thr Arg Phe Thr Gly Gln His Phe
        595                 600                 605
Cys Gly Gly Thr Leu Ile Ala Pro Glu Trp Val Leu Thr Ala Ala His
    610                 615                 620
Cys Leu Glu Lys Ser Ser Arg Pro Glu Phe Tyr Lys Val Ile Leu Gly
625                 630                 635                 640
Ala His Glu Glu Tyr Ile Arg Gly Leu Asp Val Gln Glu Ile Ser Val
                645                 650                 655
Ala Lys Leu Ile Leu Glu Pro Asn Asn Arg Asp Ile Ala Leu Leu Lys
            660                 665                 670
Leu Ser Arg Pro Ala Thr Ile Thr Asp Lys Val Ile Pro Ala Cys Leu
        675                 680                 685
Pro Ser Pro Asn Tyr Met Val Ala Asp Arg Thr Ile Cys Tyr Ile Thr
    690                 695                 700
Gly Trp Gly Glu Thr Gln Gly Thr Phe Gly Ala Gly Arg Leu Lys Glu
```

```
705                 710                 715                 720
Ala Gln Leu Pro Val Ile Glu Asn Lys Val Cys Asn Arg Val Glu Tyr
                725                 730                 735
Leu Asn Asn Arg Val Lys Ser Thr Glu Leu Cys Ala Gly Gln Leu Ala
            740                 745                 750
Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys
        755                 760                 765
Phe Glu Lys Asp Lys Tyr Ile Leu Gln Gly Val Thr Ser Trp Gly Leu
    770                 775                 780
Gly Cys Ala Arg Pro Asn Lys Pro Gly Val Tyr Val Arg Val Ser Arg
785                 790                 795                 800
Phe Val Asp Trp Ile Glu Arg Glu Met Arg Asn Asn
                805                 810
```

<210> 5
<211> 1083
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)...(1083)

<400> 5

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tat ctc tca gag tgc aag act ggg aat gga aag aac tac aga ggg acg       48
Tyr Leu Ser Glu Cys Lys Thr Gly Asn Gly Lys Asn Tyr Arg Gly Thr
 1               5                  10                  15

atg tcc aaa aca aaa aat ggc atc acc tgt caa aaa tgg agt tcc act       96
Met Ser Lys Thr Lys Asn Gly Ile Thr Cys Gln Lys Trp Ser Ser Thr
            20                  25                  30

tct ccc cac aga cct aga ttc tca cct gct aca cac ccc tca gag gga      144
Ser Pro His Arg Pro Arg Phe Ser Pro Ala Thr His Pro Ser Glu Gly
        35                  40                  45

ctg gag gag aac tac tgc agg aat cca gac aac gat ccg cag ggg ccc      192
Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Pro Gln Gly Pro
    50                  55                  60

tgg tgc tat act act gat cca gaa aag aga tat gac tac tgc gac att      240
Trp Cys Tyr Thr Thr Asp Pro Glu Lys Arg Tyr Asp Tyr Cys Asp Ile
65                  70                  75                  80

ctt gag tgt gaa gag gaa tgt atg cat tgc agt gga gaa aac tat gac      288
Leu Glu Cys Glu Glu Glu Cys Met His Cys Ser Gly Glu Asn Tyr Asp
                85                  90                  95

ggc aaa att tcc aag acc atg tct gga ctg gaa tgc cag gcc tgg gac      336
Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Glu Cys Gln Ala Trp Asp
            100                 105                 110

tct cag agc cca cac gct cat gga tac att cct tcc aaa ttt cca aac      384
Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ser Lys Phe Pro Asn
        115                 120                 125
```

```
aag aac ctg aag aag aat tac tgt cgt aac ccc gat agg gag ctg cgg      432
Lys Asn Leu Lys Lys Asn Tyr Cys Arg Asn Pro Asp Arg Glu Leu Arg
    130                 135                 140

cct tgg tgt ttc acc acc gac ccc aac aag cgc tgg gaa ctt tgc gac      480
Pro Trp Cys Phe Thr Thr Asp Pro Asn Lys Arg Trp Glu Leu Cys Asp
145                 150                 155                 160

atc ccc cgc tgc aca aca cct cca cca tct tct ggt ccc acc tac cag      528
Ile Pro Arg Cys Thr Thr Pro Pro Pro Ser Ser Gly Pro Thr Tyr Gln
                165                 170                 175

tgt ctg aag gga aca ggt gaa aac tat cgc ggg aat gtg gct gtt acc      576
Cys Leu Lys Gly Thr Gly Glu Asn Tyr Arg Gly Asn Val Ala Val Thr
            180                 185                 190

gtt tcc ggg cac acc tgt cag cac tgg agt gca cag acc cct cac aca      624
Val Ser Gly His Thr Cys Gln His Trp Ser Ala Gln Thr Pro His Thr
        195                 200                 205

cat aac agg aca cca gaa aac ttc ccc tgc aaa aat ttg gat gaa aac      672
His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Asp Glu Asn
    210                 215                 220

tac tgc cgc aat cct gac gga aaa agg gcc cca tgg tgc cat aca acc      720
Tyr Cys Arg Asn Pro Asp Gly Lys Arg Ala Pro Trp Cys His Thr Thr
225                 230                 235                 240

aac agc caa gtg cgg tgg gag tac tgt aag ata ccg tcc tgt gac tcc      768
Asn Ser Gln Val Arg Trp Glu Tyr Cys Lys Ile Pro Ser Cys Asp Ser
                245                 250                 255

tcc cca gta tcc acg gaa caa ttg gct ccc aca gca cca cct gag cta      816
Ser Pro Val Ser Thr Glu Gln Leu Ala Pro Thr Ala Pro Pro Glu Leu
            260                 265                 270

acc cct gtg gtc cag gac tgc tac cat ggt gat gga cag agc tac cga      864
Thr Pro Val Val Gln Asp Cys Tyr His Gly Asp Gly Gln Ser Tyr Arg
        275                 280                 285

ggc aca tcc tcc acc acc acc aca gga aag aag tgt cag tct tgg tca      912
Gly Thr Ser Ser Thr Thr Thr Thr Gly Lys Lys Cys Gln Ser Trp Ser
    290                 295                 300

tct atg aca cca cac cgg cac cag aag acc cca gaa aac tac cca aat      960
Ser Met Thr Pro His Arg His Gln Lys Thr Pro Glu Asn Tyr Pro Asn
305                 310                 315                 320

gct ggc ctg aca atg aac tac tgc agg aat cca gat gcc gat aaa ggc     1008
Ala Gly Leu Thr Met Asn Tyr Cys Arg Asn Pro Asp Ala Asp Lys Gly
                325                 330                 335

ccc tgg tgt ttt acc aca gac ccc agc gtc agg tgg gag tac tgc aac     1056
Pro Trp Cys Phe Thr Thr Asp Pro Ser Val Arg Trp Glu Tyr Cys Asn
```

```
            340                 345                 350

ctg aaa aaa tgc tca gga aca gaa gcg                                  1083
Leu Lys Lys Cys Ser Gly Thr Glu Ala
        355                 360


      <210> 6
      <211> 361
      <212> PRT
      <213> Homo sapiens

      <400> 6
Tyr Leu Ser Glu Cys Lys Thr Gly Asn Gly Lys Asn Tyr Arg Gly Thr
 1               5                  10                  15
Met Ser Lys Thr Lys Asn Gly Ile Thr Cys Gln Lys Trp Ser Ser Thr
            20                  25                  30
Ser Pro His Arg Pro Arg Phe Ser Pro Ala Thr His Pro Ser Glu Gly
        35                  40                  45
Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Pro Gln Gly Pro
    50                  55                  60
Trp Cys Tyr Thr Thr Asp Pro Glu Lys Arg Tyr Asp Tyr Cys Asp Ile
65                  70                  75                  80
Leu Glu Cys Glu Glu Glu Cys Met His Cys Ser Gly Glu Asn Tyr Asp
                85                  90                  95
Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Glu Cys Gln Ala Trp Asp
            100                 105                 110
Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ser Lys Phe Pro Asn
        115                 120                 125
Lys Asn Leu Lys Lys Asn Tyr Cys Arg Asn Pro Asp Arg Glu Leu Arg
    130                 135                 140
Pro Trp Cys Phe Thr Thr Asp Pro Asn Lys Arg Trp Glu Leu Cys Asp
145                 150                 155                 160
Ile Pro Arg Cys Thr Thr Pro Pro Pro Ser Ser Gly Pro Thr Tyr Gln
                165                 170                 175
Cys Leu Lys Gly Thr Gly Glu Asn Tyr Arg Gly Asn Val Ala Val Thr
            180                 185                 190
Val Ser Gly His Thr Cys Gln His Trp Ser Ala Gln Thr Pro His Thr
        195                 200                 205
His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Asp Glu Asn
    210                 215                 220
Tyr Cys Arg Asn Pro Asp Gly Lys Arg Ala Pro Trp Cys His Thr Thr
225                 230                 235                 240
Asn Ser Gln Val Arg Trp Glu Tyr Cys Lys Ile Pro Ser Cys Asp Ser
                245                 250                 255
Ser Pro Val Ser Thr Glu Gln Leu Ala Pro Thr Ala Pro Pro Glu Leu
            260                 265                 270
Thr Pro Val Val Gln Asp Cys Tyr His Gly Asp Gly Gln Ser Tyr Arg
        275                 280                 285
Gly Thr Ser Ser Thr Thr Thr Thr Gly Lys Lys Cys Gln Ser Trp Ser
    290                 295                 300
Ser Met Thr Pro His Arg His Gln Lys Thr Pro Glu Asn Tyr Pro Asn
305                 310                 315                 320
Ala Gly Leu Thr Met Asn Tyr Cys Arg Asn Pro Asp Ala Asp Lys Gly
                325                 330                 335
```

```
Pro Trp Cys Phe Thr Thr Asp Pro Ser Val Arg Trp Glu Tyr Cys Asn
            340                 345                 350
Leu Lys Lys Cys Ser Gly Thr Glu Ala
        355                 360
```

<210> 7
<211> 1086
<212> DNA
<213> Mus musculus

<220>
<221> CDS
<222> (1)...(1086)

<400> 7

```
gtg tat ctg tca gaa tgt aag acc ggc atc ggc aac ggc tac aga gga        48
Val Tyr Leu Ser Glu Cys Lys Thr Gly Ile Gly Asn Gly Tyr Arg Gly
 1               5                  10                  15

acc atg tcc agg aca aag agt ggt gtt gcc tgt caa aag tgg ggt gcc        96
Thr Met Ser Arg Thr Lys Ser Gly Val Ala Cys Gln Lys Trp Gly Ala
             20                  25                  30

acg ttc ccc cac gta ccc aac tac tct ccc agt aca cat ccc aat gag       144
Thr Phe Pro His Val Pro Asn Tyr Ser Pro Ser Thr His Pro Asn Glu
         35                  40                  45

gga cta gaa gag aac tac tgt agg aac cca gac aat gat gaa caa ggg       192
Gly Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Glu Gln Gly
     50                  55                  60

cct tgg tgc tac act aca gat ccg gac aag aga tat gac tac tgc aac       240
Pro Trp Cys Tyr Thr Thr Asp Pro Asp Lys Arg Tyr Asp Tyr Cys Asn
 65                  70                  75                  80

att cct gaa tgt gaa gag gaa tgc atg tac tgc agt gga gaa aag tat       288
Ile Pro Glu Cys Glu Glu Glu Cys Met Tyr Cys Ser Gly Glu Lys Tyr
                 85                  90                  95

gag ggc aaa atc tcc aag acc atg tct gga ctt gac tgc cag gcc tgg       336
Glu Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Asp Cys Gln Ala Trp
            100                 105                 110

gat tct cag agc cca cat gct cat gga tac atc cct gcc aaa ttt cca       384
Asp Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ala Lys Phe Pro
        115                 120                 125

agc aag aac ctg aag atg aat tat tgc cac aac cct gac ggg gag cca       432
Ser Lys Asn Leu Lys Met Asn Tyr Cys His Asn Pro Asp Gly Glu Pro
    130                 135                 140

agg ccc tgg tgc ttc aca aca gac ccc acc aaa cgc tgg gaa tac tgt       480
Arg Pro Trp Cys Phe Thr Thr Asp Pro Thr Lys Arg Trp Glu Tyr Cys
145                 150                 155                 160
```

```
gac atc ccc cgc tgc aca aca ccc ccg ccc cca ccc agc cca acc tac      528
Asp Ile Pro Arg Cys Thr Thr Pro Pro Pro Pro Pro Ser Pro Thr Tyr
                165                 170                 175

caa tgt ctg aaa gga aga ggt gaa aat tac cga ggg acc gtg tct gtc      576
Gln Cys Leu Lys Gly Arg Gly Glu Asn Tyr Arg Gly Thr Val Ser Val
            180                 185                 190

acc gtg tct ggg aaa acc tgt cag cgc tgg agt gag caa acc cct cat      624
Thr Val Ser Gly Lys Thr Cys Gln Arg Trp Ser Glu Gln Thr Pro His
        195                 200                 205

agg cac aac agg aca cca gaa aat ttc ccc tgc aaa aat ctg gaa gag      672
Arg His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Glu Glu
    210                 215                 220

aac tac tgc cgg aac cca gat gga gaa act gct ccc tgg tgc tat acc      720
Asn Tyr Cys Arg Asn Pro Asp Gly Glu Thr Ala Pro Trp Cys Tyr Thr
225                 230                 235                 240

act gac agc cag ctg agg tgg gag tac tgt gag att cca tcc tgc gag      768
Thr Asp Ser Gln Leu Arg Trp Glu Tyr Cys Glu Ile Pro Ser Cys Glu
                245                 250                 255

tcc tca gca tca cca gac cag tca gat tcc tca gtt cca cca gag gag      816
Ser Ser Ala Ser Pro Asp Gln Ser Asp Ser Ser Val Pro Pro Glu Glu
            260                 265                 270

caa aca cct gtg gtc cag gaa tgc tac cag agc gat ggg cag agc tat      864
Gln Thr Pro Val Val Gln Glu Cys Tyr Gln Ser Asp Gly Gln Ser Tyr
        275                 280                 285

cgg ggt aca tcg tcc act acc atc aca ggg aag aag tgc cag tcc tgg      912
Arg Gly Thr Ser Ser Thr Thr Ile Thr Gly Lys Lys Cys Gln Ser Trp
    290                 295                 300

gca gct atg ttt cca cac agg cat tcg aag acc cca gag aac ttc cca      960
Ala Ala Met Phe Pro His Arg His Ser Lys Thr Pro Glu Asn Phe Pro
305                 310                 315                 320

gat gct ggc ttg gag atg aac tac tgc agg aac ccg gat ggt gac aag     1008
Asp Ala Gly Leu Glu Met Asn Tyr Cys Arg Asn Pro Asp Gly Asp Lys
                325                 330                 335

ggc cct tgg tgc tac acc act gac ccg agc gtc agg tgg gaa tac tgc     1056
Gly Pro Trp Cys Tyr Thr Thr Asp Pro Ser Val Arg Trp Glu Tyr Cys
            340                 345                 350

aac ctg aag cgg tgc tca gag aca gga ggg                             1086
Asn Leu Lys Arg Cys Ser Glu Thr Gly Gly
        355                 360
```

<210> 8
<211> 362

<212> PRT
<213> Mus musculus

<400> 8

```
Val Tyr Leu Ser Glu Cys Lys Thr Gly Ile Gly Asn Gly Tyr Arg Gly
 1               5                  10                  15
Thr Met Ser Arg Thr Lys Ser Gly Val Ala Cys Gln Lys Trp Gly Ala
            20                  25                  30
Thr Phe Pro His Val Pro Asn Tyr Ser Pro Ser Thr His Pro Asn Glu
        35                  40                  45
Gly Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Glu Gln Gly
    50                  55                  60
Pro Trp Cys Tyr Thr Thr Asp Pro Asp Lys Arg Tyr Asp Tyr Cys Asn
65                  70                  75                  80
Ile Pro Glu Cys Glu Glu Glu Cys Met Tyr Cys Ser Gly Glu Lys Tyr
                85                  90                  95
Glu Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Asp Cys Gln Ala Trp
            100                 105                 110
Asp Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ala Lys Phe Pro
        115                 120                 125
Ser Lys Asn Leu Lys Met Asn Tyr Cys His Asn Pro Asp Gly Glu Pro
    130                 135                 140
Arg Pro Trp Cys Phe Thr Thr Asp Pro Thr Lys Arg Trp Glu Tyr Cys
145                 150                 155                 160
Asp Ile Pro Arg Cys Thr Thr Pro Pro Pro Pro Pro Ser Pro Thr Tyr
                165                 170                 175
Gln Cys Leu Lys Gly Arg Gly Glu Asn Tyr Arg Gly Thr Val Ser Val
            180                 185                 190
Thr Val Ser Gly Lys Thr Cys Gln Arg Trp Ser Glu Gln Thr Pro His
        195                 200                 205
Arg His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Glu Glu
    210                 215                 220
Asn Tyr Cys Arg Asn Pro Asp Gly Glu Thr Ala Pro Trp Cys Tyr Thr
225                 230                 235                 240
Thr Asp Ser Gln Leu Arg Trp Glu Tyr Cys Glu Ile Pro Ser Cys Glu
                245                 250                 255
Ser Ser Ala Ser Pro Asp Gln Ser Asp Ser Ser Val Pro Pro Glu Glu
            260                 265                 270
Gln Thr Pro Val Val Gln Glu Cys Tyr Gln Ser Asp Gly Gln Ser Tyr
        275                 280                 285
Arg Gly Thr Ser Ser Thr Thr Ile Thr Gly Lys Lys Cys Gln Ser Trp
    290                 295                 300
Ala Ala Met Phe Pro His Arg His Ser Lys Thr Pro Glu Asn Phe Pro
305                 310                 315                 320
Asp Ala Gly Leu Glu Met Asn Tyr Cys Arg Asn Pro Asp Gly Asp Lys
                325                 330                 335
Gly Pro Trp Cys Tyr Thr Thr Asp Pro Ser Val Arg Trp Glu Tyr Cys
            340                 345                 350
Asn Leu Lys Arg Cys Ser Glu Thr Gly Gly
        355                 360
```

<210> 9
<211> 552
<212> DNA
<213> Mus musculus

<220>
<221> CDS
<222> (1)...(552)

<400> 9

```
cat act cat cag gac ttt cag cca gtg ctc cac ctg gtg gca ctg aac        48
His Thr His Gln Asp Phe Gln Pro Val Leu His Leu Val Ala Leu Asn
 1               5                  10                  15

acc ccc ctg tct gga ggc atg cgt ggt atc cgt gga gca gat ttc cag        96
Thr Pro Leu Ser Gly Gly Met Arg Gly Ile Arg Gly Ala Asp Phe Gln
            20                  25                  30

tgc ttc cag caa gcc cga gcc gtg ggg ctg tcg ggc acc ttc cgg gct       144
Cys Phe Gln Gln Ala Arg Ala Val Gly Leu Ser Gly Thr Phe Arg Ala
        35                  40                  45

ttc ctg tcc tct agg ctg cag gat ctc tat agc atc gtg cgc cgt gct       192
Phe Leu Ser Ser Arg Leu Gln Asp Leu Tyr Ser Ile Val Arg Arg Ala
    50                  55                  60

gac cgg ggg tct gtg ccc atc gtc aac ctg aag gac gag gtg cta tct       240
Asp Arg Gly Ser Val Pro Ile Val Asn Leu Lys Asp Glu Val Leu Ser
65                  70                  75                  80

ccc agc tgg gac tcc ctg ttt tct ggc tcc cag ggt caa gtg caa ccc       288
Pro Ser Trp Asp Ser Leu Phe Ser Gly Ser Gln Gly Gln Val Gln Pro
                85                  90                  95

ggg gcc cgc atc ttt tct ttt gac ggc aga gat gtc ctg aga cac cca       336
Gly Ala Arg Ile Phe Ser Phe Asp Gly Arg Asp Val Leu Arg His Pro
            100                 105                 110

gcc tgg ccg cag aag agc gta tgg cac ggc tcg gac ccc agt ggg cgg       384
Ala Trp Pro Gln Lys Ser Val Trp His Gly Ser Asp Pro Ser Gly Arg
        115                 120                 125

agg ctg atg gag agt tac tgt gag aca tgg cga act gaa act act ggg       432
Arg Leu Met Glu Ser Tyr Cys Glu Thr Trp Arg Thr Glu Thr Thr Gly
    130                 135                 140

gct aca ggt cag gcc tcc tcc ctg ctg tca ggc agg ctc ctg gaa cag       480
Ala Thr Gly Gln Ala Ser Ser Leu Leu Ser Gly Arg Leu Leu Glu Gln
145                 150                 155                 160

aaa gct gcg agc tgc cac aac agc tac atc gtc ctg tgc att gag aat       528
Lys Ala Ala Ser Cys His Asn Ser Tyr Ile Val Leu Cys Ile Glu Asn
                165                 170                 175

agc ttc atg acc tct ttc tcc aaa                                      552
Ser Phe Met Thr Ser Phe Ser Lys
            180
```

<210> 10

<211> 184
<212> PRT
<213> Mus musculus

<400> 10

```
His Thr His Gln Asp Phe Gln Pro Val Leu His Leu Val Ala Leu Asn
 1               5                  10                  15
Thr Pro Leu Ser Gly Gly Met Arg Gly Ile Arg Gly Ala Asp Phe Gln
            20                  25                  30
Cys Phe Gln Gln Ala Arg Ala Val Gly Leu Ser Gly Thr Phe Arg Ala
        35                  40                  45
Phe Leu Ser Ser Arg Leu Gln Asp Leu Tyr Ser Ile Val Arg Arg Ala
    50                  55                  60
Asp Arg Gly Ser Val Pro Ile Val Asn Leu Lys Asp Glu Val Leu Ser
65                  70                  75                  80
Pro Ser Trp Asp Ser Leu Phe Ser Gly Ser Gln Gly Gln Val Gln Pro
                85                  90                  95
Gly Ala Arg Ile Phe Ser Phe Asp Gly Arg Asp Val Leu Arg His Pro
            100                 105                 110
Ala Trp Pro Gln Lys Ser Val Trp His Gly Ser Asp Pro Ser Gly Arg
        115                 120                 125
Arg Leu Met Glu Ser Tyr Cys Glu Thr Trp Arg Thr Glu Thr Thr Gly
    130                 135                 140
Ala Thr Gly Gln Ala Ser Ser Leu Leu Ser Gly Arg Leu Leu Glu Gln
145                 150                 155                 160
Lys Ala Ala Ser Cys His Asn Ser Tyr Ile Val Leu Cys Ile Glu Asn
                165                 170                 175
Ser Phe Met Thr Ser Phe Ser Lys
            180
```

<210> 11
<211> 1414
<212> DNA
<213> Mus musculus

<220>
<221> CDS
<222> (1)...(1414)

<400> 11

```
atg gac cat aag gaa gta atc ctt ctg ttt ctc ttg ctt ctg aaa cca        48
Met Asp His Lys Glu Val Ile Leu Leu Phe Leu Leu Leu Leu Lys Pro
 1               5                  10                  15

gga caa ggg gac tcg ctg gat ggc tac ata agc aca caa ggg gct tca        96
Gly Gln Gly Asp Ser Leu Asp Gly Tyr Ile Ser Thr Gln Gly Ala Ser
            20                  25                  30

ctg ttc agt ctc acc aag aag cag ctc gca gca gga ggt gtc tcg gac       144
Leu Phe Ser Leu Thr Lys Lys Gln Leu Ala Ala Gly Gly Val Ser Asp
        35                  40                  45

tgt ttg gcc aaa tgt gaa ggg gaa aca gac ttt gtc tgc agg tca ttc       192
Cys Leu Ala Lys Cys Glu Gly Glu Thr Asp Phe Val Cys Arg Ser Phe
    50                  55                  60
```

```
cag tac cac agc aaa gag cag caa tgc gtg atc atg gcg gag aac agc      240
Gln Tyr His Ser Lys Glu Gln Gln Cys Val Ile Met Ala Glu Asn Ser
 65                  70                  75                  80

aag act tcc tcc atc atc cgg atg aga gac gtc atc tta ttc gaa aag      288
Lys Thr Ser Ser Ile Ile Arg Met Arg Asp Val Ile Leu Phe Glu Lys
                85                  90                  95

aga gtg tat ctg tca gaa tgt aag acc ggc atc ggc aac ggc tac aga      336
Arg Val Tyr Leu Ser Glu Cys Lys Thr Gly Ile Gly Asn Gly Tyr Arg
            100                 105                 110

gga acc atg tcc agg aca aag agt ggt gtt gcc tgt caa aag tgg ggt      384
Gly Thr Met Ser Arg Thr Lys Ser Gly Val Ala Cys Gln Lys Trp Gly
        115                 120                 125

gcc acg ttc ccc cac gta ccc aac tac tct ccc agt aca cat ccc aat      432
Ala Thr Phe Pro His Val Pro Asn Tyr Ser Pro Ser Thr His Pro Asn
    130                 135                 140

gag gga cta gaa gag aac tac tgt agg aac cca gac aat gat gaa caa      480
Glu Gly Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Glu Gln
145                 150                 155                 160

ggg cct tgg tgc tac act aca gat ccg gac aag aga tat gac tac tgc      528
Gly Pro Trp Cys Tyr Thr Thr Asp Pro Asp Lys Arg Tyr Asp Tyr Cys
                165                 170                 175

aac att cct gaa tgt gaa gag gaa tgc atg tac tgc agt gga gaa aag      576
Asn Ile Pro Glu Cys Glu Glu Glu Cys Met Tyr Cys Ser Gly Glu Lys
            180                 185                 190

tat gag ggc aaa atc tcc aag acc atg tct gga ctt gac tgc cag gcc      624
Tyr Glu Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Asp Cys Gln Ala
        195                 200                 205

tgg gat tct cag agc cca cat gct cat gga tac atc cct gcc aaa ttt      672
Trp Asp Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ala Lys Phe
    210                 215                 220

cca agc aag aac ctg aag atg aat tat tgc cac aac cct gac ggg gag      720
Pro Ser Lys Asn Leu Lys Met Asn Tyr Cys His Asn Pro Asp Gly Glu
225                 230                 235                 240

cca agg ccc tgg tgc ttc aca aca gac ccc acc aaa cgc tgg gaa tac      768
Pro Arg Pro Trp Cys Phe Thr Thr Asp Pro Thr Lys Arg Trp Glu Tyr
                245                 250                 255

tgt gac atc ccc cgc tgc aca aca ccc ccg ccc cca ccc agc cca acc      816
Cys Asp Ile Pro Arg Cys Thr Thr Pro Pro Pro Pro Pro Ser Pro Thr
            260                 265                 270

tac caa tgt ctg aaa gga aga ggt gaa aat tac cga ggg acc gtg tct      864
Tyr Gln Cys Leu Lys Gly Arg Gly Glu Asn Tyr Arg Gly Thr Val Ser
```

```
        275                 280                 285

gtc acc gtg tct ggg aaa acc tgt cag cgc tgg agt gag caa acc cct      912
Val Thr Val Ser Gly Lys Thr Cys Gln Arg Trp Ser Glu Gln Thr Pro
    290                 295                 300

cat agg cac aac agg aca cca gaa aat ttc ccc tgc aaa aat ctg gaa      960
His Arg His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Glu
305                 310                 315                 320

gag aac tac tgc cgg aac cca gat gga gaa act gct ccc tgg tgc tat     1008
Glu Asn Tyr Cys Arg Asn Pro Asp Gly Glu Thr Ala Pro Trp Cys Tyr
                325                 330                 335

acc act gac agc cag ctg agg tgg gag tac tgt gag att cca tcc tgc     1056
Thr Thr Asp Ser Gln Leu Arg Trp Glu Tyr Cys Glu Ile Pro Ser Cys
            340                 345                 350

gag tcc tca gca tca cca gac cag tca gat tcc tca gtt cca cca gag     1104
Glu Ser Ser Ala Ser Pro Asp Gln Ser Asp Ser Ser Val Pro Pro Glu
        355                 360                 365

gag caa aca cct gtg gtc cag gaa tgc tac cag agc gat ggg cag agc     1152
Glu Gln Thr Pro Val Val Gln Glu Cys Tyr Gln Ser Asp Gly Gln Ser
    370                 375                 380

tat cgg ggt aca tcg tcc act acc atc aca ggg aag aag tgc cag tcc     1200
Tyr Arg Gly Thr Ser Ser Thr Thr Ile Thr Gly Lys Lys Cys Gln Ser
385                 390                 395                 400

tgg gca gct atg ttt cca cac agg cat tcg aag acc cca gag aac ttc     1248
Trp Ala Ala Met Phe Pro His Arg His Ser Lys Thr Pro Glu Asn Phe
                405                 410                 415

cca gat gct ggc ttg gag atg aac tac tgc agg aac ccg gat ggt gac     1296
Pro Asp Ala Gly Leu Glu Met Asn Tyr Cys Arg Asn Pro Asp Gly Asp
            420                 425                 430

aag ggc cct tgg tgc tac acc act gac ccg agc gtc agg tgg gaa tac     1344
Lys Gly Pro Trp Cys Tyr Thr Thr Asp Pro Ser Val Arg Trp Glu Tyr
        435                 440                 445

tgc aac ctg aag cgg tgc tca gag aca gga ggg aat tca gac tac aag     1392
Cys Asn Leu Lys Arg Cys Ser Glu Thr Gly Gly Asn Ser Asp Tyr Lys
    450                 455                 460

gac gac gat gac aag taa taa c                                      1414
Asp Asp Asp Asp Lys  *   *
465
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<210> 12
<211> 469
<212> PRT
<213> Mus musculus

<400> 12

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Met Asp His Lys Glu Val Ile Leu Leu Phe Leu Leu Leu Leu Lys Pro
 1               5                  10                  15
Gly Gln Gly Asp Ser Leu Asp Gly Tyr Ile Ser Thr Gln Gly Ala Ser
            20                  25                  30
Leu Phe Ser Leu Thr Lys Lys Gln Leu Ala Ala Gly Gly Val Ser Asp
        35                  40                  45
Cys Leu Ala Lys Cys Glu Gly Glu Thr Asp Phe Val Cys Arg Ser Phe
    50                  55                  60
Gln Tyr His Ser Lys Glu Gln Gln Cys Val Ile Met Ala Glu Asn Ser
65                  70                  75                  80
Lys Thr Ser Ser Ile Ile Arg Met Arg Asp Val Ile Leu Phe Glu Lys
                85                  90                  95
Arg Val Tyr Leu Ser Glu Cys Lys Thr Gly Ile Gly Asn Gly Tyr Arg
            100                 105                 110
Gly Thr Met Ser Arg Thr Lys Ser Gly Val Ala Cys Gln Lys Trp Gly
        115                 120                 125
Ala Thr Phe Pro His Val Pro Asn Tyr Ser Pro Ser Thr His Pro Asn
    130                 135                 140
Glu Gly Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Glu Gln
145                 150                 155                 160
Gly Pro Trp Cys Tyr Thr Thr Asp Pro Asp Lys Arg Tyr Asp Tyr Cys
                165                 170                 175
Asn Ile Pro Glu Cys Glu Glu Glu Cys Met Tyr Cys Ser Gly Glu Lys
            180                 185                 190
Tyr Glu Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Asp Cys Gln Ala
        195                 200                 205
Trp Asp Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ala Lys Phe
    210                 215                 220
Pro Ser Lys Asn Leu Lys Met Asn Tyr Cys His Asn Pro Asp Gly Glu
225                 230                 235                 240
Pro Arg Pro Trp Cys Phe Thr Thr Asp Pro Thr Lys Arg Trp Glu Tyr
                245                 250                 255
Cys Asp Ile Pro Arg Cys Thr Thr Pro Pro Pro Pro Pro Ser Pro Thr
            260                 265                 270
Tyr Gln Cys Leu Lys Gly Arg Gly Glu Asn Tyr Arg Gly Thr Val Ser
        275                 280                 285
Val Thr Val Ser Gly Lys Thr Cys Gln Arg Trp Ser Glu Gln Thr Pro
    290                 295                 300
His Arg His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Glu
305                 310                 315                 320
Glu Asn Tyr Cys Arg Asn Pro Asp Gly Glu Thr Ala Pro Trp Cys Tyr
                325                 330                 335
Thr Thr Asp Ser Gln Leu Arg Trp Glu Tyr Cys Glu Ile Pro Ser Cys
            340                 345                 350
Glu Ser Ser Ala Ser Pro Asp Gln Ser Asp Ser Ser Val Pro Pro Glu
        355                 360                 365
Glu Gln Thr Pro Val Val Gln Glu Cys Tyr Gln Ser Asp Gly Gln Ser
    370                 375                 380
Tyr Arg Gly Thr Ser Ser Thr Thr Ile Thr Gly Lys Lys Cys Gln Ser
385                 390                 395                 400
Trp Ala Ala Met Phe Pro His Arg His Ser Lys Thr Pro Glu Asn Phe
                405                 410                 415
Pro Asp Ala Gly Leu Glu Met Asn Tyr Cys Arg Asn Pro Asp Gly Asp
            420                 425                 430
```

```
Lys Gly Pro Trp Cys Tyr Thr Thr Asp Pro Ser Val Arg Trp Glu Tyr
        435                 440                 445
Cys Asn Leu Lys Arg Cys Ser Glu Thr Gly Gly Asn Ser Asp Tyr Lys
    450                 455                 460
Asp Asp Asp Asp Lys
465
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<210> 13
<211> 661
<212> DNA
<213> Mus musculus

<220>
<221> CDS
<222> (1)...(661)

<400> 13

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atg gac cat aag gaa gta atc ctt ctg ttt ctc ttg ctt ctg aaa cca       48
Met Asp His Lys Glu Val Ile Leu Leu Phe Leu Leu Leu Lys Pro
 1               5                  10                  15

gga caa ggg gac tcg cta gat ctt gac tac aag gac gac gat gac aag       96
Gly Gln Gly Asp Ser Leu Asp Leu Asp Tyr Lys Asp Asp Asp Asp Lys
             20                  25                  30

ctt gct cat act cat cag gac ttt cag cca gtg ctc cac ctg gtg gca      144
Leu Ala His Thr His Gln Asp Phe Gln Pro Val Leu His Leu Val Ala
         35                  40                  45

ctg aac acc ccc ctg tct gga ggc atg cgt ggt atc cgt gga gca gat      192
Leu Asn Thr Pro Leu Ser Gly Gly Met Arg Gly Ile Arg Gly Ala Asp
     50                  55                  60

ttc cag tgc ttc cag caa gcc cga gcc gtg ggg ctg tcg ggc acc ttc      240
Phe Gln Cys Phe Gln Gln Ala Arg Ala Val Gly Leu Ser Gly Thr Phe
 65                  70                  75                  80

cgg gct ttc ctg tcc tct agg ctg cag gat ctc tat agc atc gtg cgc      288
Arg Ala Phe Leu Ser Ser Arg Leu Gln Asp Leu Tyr Ser Ile Val Arg
                 85                  90                  95

cgt gct gac cgg ggg tct gtg ccc atc gtc aac ctg aag gac gag gtg      336
Arg Ala Asp Arg Gly Ser Val Pro Ile Val Asn Leu Lys Asp Glu Val
            100                 105                 110

cta tct ccc agc tgg gac tcc ctg ttt tct ggc tcc cag ggt caa gtg      384
Leu Ser Pro Ser Trp Asp Ser Leu Phe Ser Gly Ser Gln Gly Gln Val
        115                 120                 125

caa ccc ggg gcc cgc atc ttt tct ttt gac ggc aga gat gtc ctg aga      432
Gln Pro Gly Ala Arg Ile Phe Ser Phe Asp Gly Arg Asp Val Leu Arg
    130                 135                 140

cac cca gcc tgg ccg cag aag agc gta tgg cac ggc tcg gac ccc agt      480
His Pro Ala Trp Pro Gln Lys Ser Val Trp His Gly Ser Asp Pro Ser
```

```
145                 150                 155                 160

ggg cgg agg ctg atg gag agt tac tgt gag aca tgg cga act gaa act      528
Gly Arg Arg Leu Met Glu Ser Tyr Cys Glu Thr Trp Arg Thr Glu Thr
                165                 170                 175

act ggg gct aca ggt cag gcc tcc tcc ctg ctg tca ggc agg ctc ctg      576
Thr Gly Ala Thr Gly Gln Ala Ser Ser Leu Leu Ser Gly Arg Leu Leu
            180                 185                 190

gaa cag aaa gct gcg agc tgc cac aac agc tac atc gtc ctg tgc att      624
Glu Gln Lys Ala Ala Ser Cys His Asn Ser Tyr Ile Val Leu Cys Ile
        195                 200                 205

gag aat agc ttc atg acc tct ttc tcc aaa taa taa c                   661
Glu Asn Ser Phe Met Thr Ser Phe Ser Lys  *   *
    210                 215
```

<210> 14
<211> 218
<212> PRT
<213> Mus musculus

<400> 14

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Met Asp His Lys Glu Val Ile Leu Leu Phe Leu Leu Leu Leu Lys Pro
 1               5                  10                  15
Gly Gln Gly Asp Ser Leu Asp Leu Asp Tyr Lys Asp Asp Asp Asp Lys
            20                  25                  30
Leu Ala His Thr His Gln Asp Phe Gln Pro Val Leu His Leu Val Ala
        35                  40                  45
Leu Asn Thr Pro Leu Ser Gly Gly Met Arg Gly Ile Arg Gly Ala Asp
    50                  55                  60
Phe Gln Cys Phe Gln Gln Ala Arg Ala Val Gly Leu Ser Gly Thr Phe
65                  70                  75                  80
Arg Ala Phe Leu Ser Ser Arg Leu Gln Asp Leu Tyr Ser Ile Val Arg
                85                  90                  95
Arg Ala Asp Arg Gly Ser Val Pro Ile Val Asn Leu Lys Asp Glu Val
            100                 105                 110
Leu Ser Pro Ser Trp Asp Ser Leu Phe Ser Gly Ser Gln Gly Gln Val
        115                 120                 125
Gln Pro Gly Ala Arg Ile Phe Ser Phe Asp Gly Arg Asp Val Leu Arg
    130                 135                 140
His Pro Ala Trp Pro Gln Lys Ser Val Trp His Gly Ser Asp Pro Ser
145                 150                 155                 160
Gly Arg Arg Leu Met Glu Ser Tyr Cys Glu Thr Trp Arg Thr Glu Thr
                165                 170                 175
Thr Gly Ala Thr Gly Gln Ala Ser Ser Leu Leu Ser Gly Arg Leu Leu
            180                 185                 190
Glu Gln Lys Ala Ala Ser Cys His Asn Ser Tyr Ile Val Leu Cys Ile
        195                 200                 205
Glu Asn Ser Phe Met Thr Ser Phe Ser Lys
    210                 215
```

<210> 15

<211> 1747
<212> DNA
<213> Mus musculus

<220>
<221> CDS
<222> (1)...(1747)

<400> 15

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atg gac cat aag gaa gta atc ctt ctg ttt ctc ttg ctt ctg aaa cca        48
Met Asp His Lys Glu Val Ile Leu Leu Phe Leu Leu Leu Leu Lys Pro
 1               5                  10                  15

gga caa ggg gac tcg ctg gat ggc tac ata agc aca caa ggg gct tca        96
Gly Gln Gly Asp Ser Leu Asp Gly Tyr Ile Ser Thr Gln Gly Ala Ser
            20                  25                  30

ctg ttc agt ctc acc aag aag cag ctc gca gca gga ggt gtc tcg gac       144
Leu Phe Ser Leu Thr Lys Lys Gln Leu Ala Ala Gly Gly Val Ser Asp
        35                  40                  45

tgt ttg gcc aaa tgt gaa ggg gaa aca gac ttt gtc tgc agg tca ttc       192
Cys Leu Ala Lys Cys Glu Gly Glu Thr Asp Phe Val Cys Arg Ser Phe
    50                  55                  60

cag tac cac agc aaa gag cag caa tgc gtg atc atg gcg gag aac agc       240
Gln Tyr His Ser Lys Glu Gln Gln Cys Val Ile Met Ala Glu Asn Ser
65                  70                  75                  80

aag act tcc tcc atc atc cgg atg aga gac gtc atc tta ttc gaa aag       288
Lys Thr Ser Ser Ile Ile Arg Met Arg Asp Val Ile Leu Phe Glu Lys
                85                  90                  95

aga gtg tat ctg tca gaa tgt aag acc ggc atc ggc aac ggc tac aga       336
Arg Val Tyr Leu Ser Glu Cys Lys Thr Gly Ile Gly Asn Gly Tyr Arg
            100                 105                 110

gga acc atg tcc agg aca aag agt ggt gtt gcc tgt caa aag tgg ggt       384
Gly Thr Met Ser Arg Thr Lys Ser Gly Val Ala Cys Gln Lys Trp Gly
        115                 120                 125

gcc acg ttc ccc cac gta ccc aac tac tct ccc agt aca cat ccc aat       432
Ala Thr Phe Pro His Val Pro Asn Tyr Ser Pro Ser Thr His Pro Asn
    130                 135                 140

gag gga cta gaa gag aac tac tgt agg aac cca gac aat gat gaa caa       480
Glu Gly Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Glu Gln
145                 150                 155                 160

ggg cct tgg tgc tac act aca gat ccg gac aag aga tat gac tac tgc       528
Gly Pro Trp Cys Tyr Thr Thr Asp Pro Asp Lys Arg Tyr Asp Tyr Cys
                165                 170                 175

aac att cct gaa tgt gaa gag gaa tgc atg tac tgc agt gga gaa aag       576
Asn Ile Pro Glu Cys Glu Glu Glu Cys Met Tyr Cys Ser Gly Glu Lys
```

```
            180                 185                 190

tat gag ggc aaa atc tcc aag acc atg tct gga ctt gac tgc cag gcc      624
Tyr Glu Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Asp Cys Gln Ala
        195                 200                 205

tgg gat tct cag agc cca cat gct cat gga tac atc cct gcc aaa ttt      672
Trp Asp Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ala Lys Phe
    210                 215                 220

cca agc aag aac ctg aag atg aat tat tgc cac aac cct gac ggg gag      720
Pro Ser Lys Asn Leu Lys Met Asn Tyr Cys His Asn Pro Asp Gly Glu
225                 230                 235                 240

cca agg ccc tgg tgc ttc aca aca gac ccc acc aaa cgc tgg gaa tac      768
Pro Arg Pro Trp Cys Phe Thr Thr Asp Pro Thr Lys Arg Trp Glu Tyr
                245                 250                 255

tgt gac atc ccc cgc tgc aca aca ccc ccg ccc cca ccc agc cca acc      816
Cys Asp Ile Pro Arg Cys Thr Thr Pro Pro Pro Pro Pro Ser Pro Thr
            260                 265                 270

tac caa tgt ctg aaa gga aga ggt gaa aat tac cga ggg acc gtg tct      864
Tyr Gln Cys Leu Lys Gly Arg Gly Glu Asn Tyr Arg Gly Thr Val Ser
        275                 280                 285

gtc acc gtg tct ggg aaa acc tgt cag cgc tgg agt gag caa acc cct      912
Val Thr Val Ser Gly Lys Thr Cys Gln Arg Trp Ser Glu Gln Thr Pro
    290                 295                 300

cat agg cac aac agg aca cca gaa aat ttc ccc tgc aaa aat ctg gaa      960
His Arg His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Glu
305                 310                 315                 320

gag aac tac tgc cgg aac cca gat gga gaa act gct ccc tgg tgc tat     1008
Glu Asn Tyr Cys Arg Asn Pro Asp Gly Glu Thr Ala Pro Trp Cys Tyr
                325                 330                 335

acc act gac agc cag ctg agg tgg gag tac tgt gag att cca tcc tgc     1056
Thr Thr Asp Ser Gln Leu Arg Trp Glu Tyr Cys Glu Ile Pro Ser Cys
            340                 345                 350

gag tcc tca gca tca cca gac cag tca gat tcc tca gtt cca cca gag     1104
Glu Ser Ser Ala Ser Pro Asp Gln Ser Asp Ser Ser Val Pro Pro Glu
        355                 360                 365

gag caa aca cct gtg gga ggg aat tgc ggc ggt gga tca ggt ggc gga     1152
Glu Gln Thr Pro Val Gly Gly Asn Cys Gly Gly Gly Ser Gly Gly Gly
    370                 375                 380

gat ctt gac tac aag gac gac gat gac aag ctt gct cat act cat cag     1200
Asp Leu Asp Tyr Lys Asp Asp Asp Asp Lys Leu Ala His Thr His Gln
385                 390                 395                 400

gac ttt cag cca gtg ctc cac ctg gtg gca ctg aac acc ccc ctg tct     1248
```

```
Asp Phe Gln Pro Val Leu His Leu Val Ala Leu Asn Thr Pro Leu Ser
                405                 410                 415

gga ggc atg cgt ggt atc cgt gga gca gat ttc cag tgc ttc cag caa      1296
Gly Gly Met Arg Gly Ile Arg Gly Ala Asp Phe Gln Cys Phe Gln Gln
            420                 425                 430

gcc cga gcc gtg ggg ctg tcg ggc acc ttc cgg gct ttc ctg tcc tct      1344
Ala Arg Ala Val Gly Leu Ser Gly Thr Phe Arg Ala Phe Leu Ser Ser
        435                 440                 445

agg ctg cag gat ctc tat agc atc gtg cgc cgt gct gac cgg ggg tct      1392
Arg Leu Gln Asp Leu Tyr Ser Ile Val Arg Arg Ala Asp Arg Gly Ser
    450                 455                 460

gtg ccc atc gtc aac ctg aag gac gag gtg cta tct ccc agc tgg gac      1440
Val Pro Ile Val Asn Leu Lys Asp Glu Val Leu Ser Pro Ser Trp Asp
465                 470                 475                 480

tcc ctg ttt tct ggc tcc cag ggt caa gtg caa ccc ggg gcc cgc atc      1488
Ser Leu Phe Ser Gly Ser Gln Gly Gln Val Gln Pro Gly Ala Arg Ile
                485                 490                 495

ttt tct ttt gac ggc aga gat gtc ctg aga cac cca gcc tgg ccg cag      1536
Phe Ser Phe Asp Gly Arg Asp Val Leu Arg His Pro Ala Trp Pro Gln
            500                 505                 510

aag agc gta tgg cac ggc tcg gac ccc agt ggg cgg agg ctg atg gag      1584
Lys Ser Val Trp His Gly Ser Asp Pro Ser Gly Arg Arg Leu Met Glu
        515                 520                 525

agt tac tgt gag aca tgg cga act gaa act act ggg gct aca ggt cag      1632
Ser Tyr Cys Glu Thr Trp Arg Thr Glu Thr Thr Gly Ala Thr Gly Gln
    530                 535                 540

gcc tcc tcc ctg ctg tca ggc agg ctc ctg gaa cag aaa gct gcg agc      1680
Ala Ser Ser Leu Leu Ser Gly Arg Leu Leu Glu Gln Lys Ala Ala Ser
545                 550                 555                 560

tgc cac aac agc tac atc gtc ctg tgc att gag aat agc ttc atg acc      1728
Cys His Asn Ser Tyr Ile Val Leu Cys Ile Glu Asn Ser Phe Met Thr
                565                 570                 575

tct ttc tcc aaa taa taa c                                           1747
Ser Phe Ser Lys  *   *
            580
```

<210> 16
<211> 580
<212> PRT
<213> Mus musculus

<400> 16

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Met Asp His Lys Glu Val Ile Leu Leu Phe Leu Leu Leu Leu Lys Pro
```

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 1               5                  10                  15
Gly Gln Gly Asp Ser Leu Asp Gly Tyr Ile Ser Thr Gln Gly Ala Ser
            20                  25                  30
Leu Phe Ser Leu Thr Lys Lys Gln Leu Ala Ala Gly Gly Val Ser Asp
        35                  40                  45
Cys Leu Ala Lys Cys Glu Gly Glu Thr Asp Phe Val Cys Arg Ser Phe
    50                  55                  60
Gln Tyr His Ser Lys Glu Gln Gln Cys Val Ile Met Ala Glu Asn Ser
65                  70                  75                  80
Lys Thr Ser Ser Ile Ile Arg Met Arg Asp Val Ile Leu Phe Glu Lys
                85                  90                  95
Arg Val Tyr Leu Ser Glu Cys Lys Thr Gly Ile Gly Asn Gly Tyr Arg
            100                 105                 110
Gly Thr Met Ser Arg Thr Lys Ser Gly Val Ala Cys Gln Lys Trp Gly
        115                 120                 125
Ala Thr Phe Pro His Val Pro Asn Tyr Ser Pro Ser Thr His Pro Asn
    130                 135                 140
Glu Gly Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Glu Gln
145                 150                 155                 160
Gly Pro Trp Cys Tyr Thr Thr Asp Pro Asp Lys Arg Tyr Asp Tyr Cys
                165                 170                 175
Asn Ile Pro Glu Cys Glu Glu Glu Cys Met Tyr Cys Ser Gly Glu Lys
            180                 185                 190
Tyr Glu Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Asp Cys Gln Ala
        195                 200                 205
Trp Asp Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ala Lys Phe
    210                 215                 220
Pro Ser Lys Asn Leu Lys Met Asn Tyr Cys His Asn Pro Asp Gly Glu
225                 230                 235                 240
Pro Arg Pro Trp Cys Phe Thr Thr Asp Pro Thr Lys Arg Trp Glu Tyr
                245                 250                 255
Cys Asp Ile Pro Arg Cys Thr Thr Pro Pro Pro Pro Pro Ser Pro Thr
            260                 265                 270
Tyr Gln Cys Leu Lys Gly Arg Gly Glu Asn Tyr Arg Gly Thr Val Ser
        275                 280                 285
Val Thr Val Ser Gly Lys Thr Cys Gln Arg Trp Ser Glu Gln Thr Pro
    290                 295                 300
His Arg His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Glu
305                 310                 315                 320
Glu Asn Tyr Cys Arg Asn Pro Asp Gly Glu Thr Ala Pro Trp Cys Tyr
                325                 330                 335
Thr Thr Asp Ser Gln Leu Arg Trp Glu Tyr Cys Glu Ile Pro Ser Cys
            340                 345                 350
Glu Ser Ser Ala Ser Pro Asp Gln Ser Asp Ser Ser Val Pro Pro Glu
        355                 360                 365
Glu Gln Thr Pro Val Gly Gly Asn Cys Gly Gly Gly Ser Gly Gly Gly
    370                 375                 380
Asp Leu Asp Tyr Lys Asp Asp Asp Asp Lys Leu Ala His Thr His Gln
385                 390                 395                 400
Asp Phe Gln Pro Val Leu His Leu Val Ala Leu Asn Thr Pro Leu Ser
                405                 410                 415
Gly Gly Met Arg Gly Ile Arg Gly Ala Asp Phe Gln Cys Phe Gln Gln
            420                 425                 430
Ala Arg Ala Val Gly Leu Ser Gly Thr Phe Arg Ala Phe Leu Ser Ser
        435                 440                 445
```

```
Arg Leu Gln Asp Leu Tyr Ser Ile Val Arg Arg Ala Asp Arg Gly Ser
    450                 455                 460
Val Pro Ile Val Asn Leu Lys Asp Glu Val Leu Ser Pro Ser Trp Asp
465                 470                 475                 480
Ser Leu Phe Ser Gly Ser Gln Gly Gln Val Gln Pro Gly Ala Arg Ile
                485                 490                 495
Phe Ser Phe Asp Gly Arg Asp Val Leu Arg His Pro Ala Trp Pro Gln
            500                 505                 510
Lys Ser Val Trp His Gly Ser Asp Pro Ser Gly Arg Arg Leu Met Glu
        515                 520                 525
Ser Tyr Cys Glu Thr Trp Arg Thr Glu Thr Thr Gly Ala Thr Gly Gln
    530                 535                 540
Ala Ser Ser Leu Leu Ser Gly Arg Leu Leu Glu Gln Lys Ala Ala Ser
545                 550                 555                 560
Cys His Asn Ser Tyr Ile Val Leu Cys Ile Glu Asn Ser Phe Met Thr
                565                 570                 575
Ser Phe Ser Lys
            580
```

<210> 17
<211> 549
<212> DNA
<213> Homo sapiens

<400> 17

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cacagccacc gcgacttcca gccggtgctc cacctggttg cgctcaacag ccccctgtca      60
ggcggcatgc ggggcatccg cggggccgac ttccagtgct tccagcaggc gcgggccgtg     120
gggctggcgg gcaccttccg cgccttcctg tcctcgcgcc tgcaggacct gtacagcatc     180
gtgcgccgtg ccgaccgcgc agccgtgccc atcgtcaacc tcaaggacga gctgctgttt     240
cccagctggg aggctctgtt ctcaggctct gagggtccgc tgaagcccgg ggcacgcatc     300
ttctcctttg acggcaagga cgtcctgagg caccccacct ggccccagaa gagcgtgtgg     360
catggctcgg accccaacgg gcgcaggctg accgagagct actgtgagac gtggcggacg     420
gaggctccct cggccacggg ccaggcctcc tcgctgctgg ggggcaggct cctggggcag     480
agtgccgcga gctgccatca cgcctacatc gtgctctgca ttgagaacag cttcatgact     540
gcctccaag                                                             549
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<210> 18
<211> 183
<212> PRT
<213> Homo sapiens

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/24950

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A01N 63/00, 43/04; C12N 15/00; C07H 21/02
US CL : 424/93.1; 435/320.1; 514/44; 536/23.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/93.1; 435/320.1; 514/44; 536/23.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	US 5,792,845 A (O'REILLY et al.) 11 August 1998 (11.08.98), col. 4, lines 32-68, col. 5, lines 1-2, 51-68, col. 6, lines 1-8.	1-30, 33
Y	WO 97/23500 A1 (THE CHILDREN'S MEDICAL CENTER CORPORATION) 03 July 1997 (03.07.97), page 41, lines 3-33, page 42, lines 1-27.	4
X,P --- Y,P	WO 98/49321 A2 (RHONE-POULENC RORER) 05 November 1998 (05.11.98), page 44, 6-11, 25-33, page 45, lines 12-13, 29-35.	1, 5, 18, 20, 31 --- 2-4, 6-17, 19, 21-30, 32, 33

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 04 FEBRUARY 1999	Date of mailing of the international search report 08 MAR 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer SHIN-LIN CHEN Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/24950

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97/15666 A (THE CHILDREN'S MEDICAL CENTER CORPORATION) 01 May 1997 (01.05.97), page 20, lines 16-35, page 21, page 22, lines 1-16. page 59, lines 5-35, page 60, page 61, 1-6.	1-30, 33
Y	TANAKA, T. et al. Retroviral and adenoviral mediated transduction of angiostatin cDNA inhibits angiogenesis and tumor growth. Proceedings of the American Association for Cancer Research. March 1997 (03.97). Vol 38. page 264.	1-33
Y	WO 96/35774 A2 (THE CHILDREN'S MEDICAL CENTER CORPORATION) 14 November 1996 (14.11.96), page lines 33-36, pages 22-25, page 26, lines 1-33. pages 144-148.	1-30, 33
Y	WO 97/41824 A2(ABBOTT LABORATORIES) 13 November 1997 (13.11.97), page 5, lines 13-38, page 6, 1-18, page 60, lines 15-38, pages 61-62, page 63, lines 1-33.	1-30, 33
Y	WO 95/29242 A1 (THE CHILDREN;S MEDICAL CENTER CORPORATION) 02 November 1995 (02.11.95), page 21, lines 19-35, pages 22-27, page 28, lines 1-4. page 87, lines 4-35, page 88, page 89, lines 1-14.	1-30, 33
Y	O'REILLY, et al. Angiostatin induces and sustains dormancy of human primary tumors in mice. Nature Medicine, June 1996 (06.96), Vol. 2, No. 6, pages 689-692, especially pages 689-690.	1-30, 33
Y	O'REILLY, et al. Endostatin: An Endogenous Inhibitor of Angiogenesis and Tumor Growth. Cell, 24 January 1997 (24.01.97), Vol. 88, pages 277-285, especially pages 279-280, 282.	1-30, 33

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/24950

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

APS, STN, WPIDS, MEDLINE, CAPLUS, BIOSIS, EMBASE
search terms: angiostatin, plasminogen, endostatin, colagen(w) XVIII, inhibit?(5a)tumor(5a)growth, tumor(5a)regress?, diabet?(p)retinopathy, plasmid, viral(5a) vector.